=> fil reg; d ide l1

FILE 'REGISTRY' ENTERED AT 14:18:38 ON 20 MAR 2001

STRUCTURE FILE UPDATES: 19 MAR 2001 HIGHEST RN 328055-05-6
DICTIONARY FILE UPDATES: 19 MAR 2001 HIGHEST RN 328055-05-6

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 9000-81-1 REGISTRY
CN Esterase, acetyl choline (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Acetyl .beta.-methylcholinesterase
CN Acetylcholine acetylhydrolase
CN Acetylcholine esterase
CN Acetylcholine hydrolase
CN **Acetylcholinesterase**
CN Acetylthiocholinesterase
CN E.C. 3.1.1.7
DR 9026-02-2
MF Unspecified
CI MAN
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS, NIOSHTIC, PROMT, TOXLINE, TOXLIT, ULIDAT, USPATFULL
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
13274 REFERENCES IN FILE CA (1967 TO DATE)
168 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13291 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> fil capl; d que l24; fil medl; d que l42; d que l60; d que l44; d que l57; d que l58; d que l67; d que l72

FILE 'CAPLUS' ENTERED AT 16:19:07 ON 20 MAR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 20 Mar 2001 VOL 134 ISS 13
FILE LAST UPDATED: 19 Mar 2001 (20010319/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

The CA Lexicon is now available in the Controlled Term (/CT) field. Enter HELP LEXICON for full details.

L1	1	SEA FILE=REGISTRY ABB=ON ACETYLCHOLINESTERASE/CN
L2	18099	SEA FILE=CAPLUS ABB=ON L1 OR ACETYLCHOLINESTERASE OR (ACETYLCHOLINE)(W)(ESTERASE OR ACETYLHYDROLASE OR HYDROLASE) OR ACETYLTHIOCHOLINESTERASE OR ACETYL .BETA. METHYLCHOLINESTERASE
L3	3739	SEA FILE=CAPLUS ABB=ON L2(L)INHIBIT?/OBI
L4	641751	SEA FILE=CAPLUS ABB=ON ANIMAL#/CW
L5	116	SEA FILE=CAPLUS ABB=ON L3 AND L4
L6	4229	SEA FILE=CAPLUS ABB=ON DEPRESSION(L)MENTAL/CW
L7	1849	SEA FILE=CAPLUS ABB=ON COGNITIVE(L)(DISORDER# OR DYSFUNCTION)
L8	76	SEA FILE=CAPLUS ABB=ON COGNITIVE PROCESSING
L9	1072	SEA FILE=CAPLUS ABB=ON COGNITION/CT
L10	34899	SEA FILE=CAPLUS ABB=ON MEMORY/CW
L11	2170	SEA FILE=CAPLUS ABB=ON DISORIENT?
L12	4883	SEA FILE=CAPLUS ABB=ON CONFUS?
L13	753	SEA FILE=CAPLUS ABB=ON SOCIAL?(2A) INTERACT?
L14	1516	SEA FILE=CAPLUS ABB=ON BEHAVIOR(L)SOCIAL/OBI
L15	781	SEA FILE=CAPLUS ABB=ON SLEEP WAKE
L16	239	SEA FILE=CAPLUS ABB=ON SLEEP DISORDERS/CT
L17	1488	SEA FILE=CAPLUS ABB=ON CIRCADIAN RHYTHM/CT
L18	10	SEA FILE=CAPLUS ABB=ON INAPPROPRIATE?(2A) ELIMINAT?
L19	12164	SEA FILE=CAPLUS ABB=ON AGE RELATED

Searched by Barb O'Bryen, STIC 308-4291

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L20       24615 SEA FILE=CAPLUS ABB=ON  AGING/CW
L22         934 SEA FILE=CAPLUS ABB=ON  COGNITION ENHANCERS/CT
L23          27 SEA FILE=CAPLUS ABB=ON  L5 AND ((L6 OR L7 OR L8 OR L9 OR L10
                OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19
                OR L20) OR L22)
L24          22 SEA FILE=CAPLUS ABB=ON  L23 AND PHARMAC?/SC


FILE 'MEDLINE' ENTERED AT 16:19:11 ON 20 MAR 2001

 FILE LAST UPDATED: 27 OCT 2000 (20001027/UP). FILE COVERS 1958 TO DATE.

 MEDLINE now contains new records from the former NLM HEALTH STAR
 database. These records have an Entry Date and Update Date of 20010223.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

 The OLDMEDLINE file segment now contains data from 1958 through 1965.
 Enter HELP CONTENT for details.

 Left, right, and simultaneous left and right truncation are available in the
 Basic Index. See HELP SFIELDS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.

 MEDLINE UPDATES ARE ON HOLD UNTIL AFTER THE ANNUAL RELOAD HAS BEEN
 COMPLETED. NOTICE WILL BE GIVEN ONCE THE RELOAD IS COMPLETED AND
 RELOAD DETAILS WILL BE FOUND IN HELP RLOAD.


L26        6991 SEA FILE=MEDLINE ABB=ON  CHOLINESTERASE INHIBITORS/CT
L27         825 SEA FILE=MEDLINE ABB=ON  ACETYLCHOLINESTERASE/CT(L)AI/CT
L28       11280 SEA FILE=MEDLINE ABB=ON  COGNITION DISORDERS+NT/CT
L29       34522 SEA FILE=MEDLINE ABB=ON  DEPRESSIVE DISORDER+NT/CT
L30       27623 SEA FILE=MEDLINE ABB=ON  DEPRESSION/CT
L31        8733 SEA FILE=MEDLINE ABB=ON  MEMORY DISORDERS+NT/CT
L32        3892 SEA FILE=MEDLINE ABB=ON  CONFUSION+NT/CT
L33      106363 SEA FILE=MEDLINE ABB=ON  INTERPERSONAL RELATIONS+NT/CT
L34        7657 SEA FILE=MEDLINE ABB=ON  SOCIAL ISOLATION+NT/CT
L35          60 SEA FILE=MEDLINE ABB=ON  SLEEP DISORDERS, CIRCADIAN RHYTHM+NT/C
                T
L36         102 SEA FILE=MEDLINE ABB=ON  ELIMINATIVE BEHAVIOR, ANIMAL/CT
L37         144 SEA FILE=MEDLINE ABB=ON  (L26 OR L27) AND ((L28 OR L29 OR L30
                OR L31 OR L32 OR L33 OR L34 OR L35 OR L36))
L38         345 SEA FILE=MEDLINE ABB=ON  COMPANION ANIMAL#
L39        6919 SEA FILE=MEDLINE ABB=ON  ANIMALS, DOMESTIC/CT
L40       97071 SEA FILE=MEDLINE ABB=ON  CATS/CT
L41      211309 SEA FILE=MEDLINE ABB=ON  DOGS/CT
L42           0 SEA FILE=MEDLINE ABB=ON  L37 AND ((L38 OR L39 OR L40 OR L41))


L26        6991 SEA FILE=MEDLINE ABB=ON  CHOLINESTERASE INHIBITORS/CT
L35          60 SEA FILE=MEDLINE ABB=ON  SLEEP DISORDERS, CIRCADIAN RHYTHM+NT/C
                T
L36         102 SEA FILE=MEDLINE ABB=ON  ELIMINATIVE BEHAVIOR, ANIMAL/CT
L60           0 SEA FILE=MEDLINE ABB=ON  L26 AND (L35 OR L36)
```

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L27          825 SEA FILE=MEDLINE ABB=ON  ACETYLCHOLINESTERASE/CT(L)AI/CT
L28        11280 SEA FILE=MEDLINE ABB=ON  COGNITION DISORDERS+NT/CT
L29        34522 SEA FILE=MEDLINE ABB=ON  DEPRESSIVE DISORDER+NT/CT
L30        27623 SEA FILE=MEDLINE ABB=ON  DEPRESSION/CT
L31         8733 SEA FILE=MEDLINE ABB=ON  MEMORY DISORDERS+NT/CT
L32         3892 SEA FILE=MEDLINE ABB=ON  CONFUSION+NT/CT
L33       106363 SEA FILE=MEDLINE ABB=ON  INTERPERSONAL RELATIONS+NT/CT
L34         7657 SEA FILE=MEDLINE ABB=ON  SOCIAL ISOLATION+NT/CT
L35           60 SEA FILE=MEDLINE ABB=ON  SLEEP DISORDERS, CIRCADIAN RHYTHM+NT/C
                 T
L36          102 SEA FILE=MEDLINE ABB=ON  ELIMINATIVE BEHAVIOR, ANIMAL/CT
L44            2 SEA FILE=MEDLINE ABB=ON  L27 AND ((L28 OR L29 OR L30 OR L31 OR
                 L32 OR L33 OR L34 OR L35 OR L36))


L26          6991 SEA FILE=MEDLINE ABB=ON  CHOLINESTERASE INHIBITORS/CT
L29         34522 SEA FILE=MEDLINE ABB=ON  DEPRESSIVE DISORDER+NT/CT
L30         27623 SEA FILE=MEDLINE ABB=ON  DEPRESSION/CT
L32          3892 SEA FILE=MEDLINE ABB=ON  CONFUSION+NT/CT
L33        106363 SEA FILE=MEDLINE ABB=ON  INTERPERSONAL RELATIONS+NT/CT
L34          7657 SEA FILE=MEDLINE ABB=ON  SOCIAL ISOLATION+NT/CT
L35            60 SEA FILE=MEDLINE ABB=ON  SLEEP DISORDERS, CIRCADIAN RHYTHM+NT/C
                  T
L36           102 SEA FILE=MEDLINE ABB=ON  ELIMINATIVE BEHAVIOR, ANIMAL/CT
L45          4201 SEA FILE=MEDLINE ABB=ON  L26(L)(PD OR AD OR TU)/CT
L56            27 SEA FILE=MEDLINE ABB=ON  L45 AND (L29 OR L30 OR (L32 OR L33 OR
                  L34 OR L35 OR L36))
L57             3 SEA FILE=MEDLINE ABB=ON  ANIMAL/CT AND L56


L26          6991 SEA FILE=MEDLINE ABB=ON  CHOLINESTERASE INHIBITORS/CT
L28         11280 SEA FILE=MEDLINE ABB=ON  COGNITION DISORDERS+NT/CT
L29         34522 SEA FILE=MEDLINE ABB=ON  DEPRESSIVE DISORDER+NT/CT
L30         27623 SEA FILE=MEDLINE ABB=ON  DEPRESSION/CT
L31          8733 SEA FILE=MEDLINE ABB=ON  MEMORY DISORDERS+NT/CT
L32          3892 SEA FILE=MEDLINE ABB=ON  CONFUSION+NT/CT
L33        106363 SEA FILE=MEDLINE ABB=ON  INTERPERSONAL RELATIONS+NT/CT
L34          7657 SEA FILE=MEDLINE ABB=ON  SOCIAL ISOLATION+NT/CT
L35            60 SEA FILE=MEDLINE ABB=ON  SLEEP DISORDERS, CIRCADIAN RHYTHM+NT/C
                  T
L36           102 SEA FILE=MEDLINE ABB=ON  ELIMINATIVE BEHAVIOR, ANIMAL/CT
L45          4201 SEA FILE=MEDLINE ABB=ON  L26(L)(PD OR AD OR TU)/CT - Subheadings
L46         18033 SEA FILE=MEDLINE ABB=ON  ((L28 OR L29 OR L30 OR L31 OR L32 OR
                  L33 OR L34 OR L35 OR L36))(L)(DT OR PC)/CT - DT-drug therapy
L56            27 SEA FILE=MEDLINE ABB=ON  L45 AND (L29 OR L30 OR (L32 OR L33 OR
                  L34 OR L35 OR L36))
L58            10 SEA FILE=MEDLINE ABB=ON  L56 AND L46


L26          6991 SEA FILE=MEDLINE ABB=ON  CHOLINESTERASE INHIBITORS/CT
L34          7657 SEA FILE=MEDLINE ABB=ON  SOCIAL ISOLATION+NT/CT
L45          4201 SEA FILE=MEDLINE ABB=ON  L26(L)(PD OR AD OR TU)/CT
L67             1 SEA FILE=MEDLINE ABB=ON  L45 AND L34


L26          6991 SEA FILE=MEDLINE ABB=ON  CHOLINESTERASE INHIBITORS/CT
L28         11280 SEA FILE=MEDLINE ABB=ON  COGNITION DISORDERS+NT/CT
```

PD - pharmacology
AD - administration & dosage
TU - therapeutic use
PC - prevention & control

Searched by Barb O'Bryen, STIC 308-4291

```
L29        34522 SEA FILE=MEDLINE ABB=ON  DEPRESSIVE DISORDER+NT/CT
L30        27623 SEA FILE=MEDLINE ABB=ON  DEPRESSION/CT
L31         8733 SEA FILE=MEDLINE ABB=ON  MEMORY DISORDERS+NT/CT
L32         3892 SEA FILE=MEDLINE ABB=ON  CONFUSION+NT/CT
L33       106363 SEA FILE=MEDLINE ABB=ON  INTERPERSONAL RELATIONS+NT/CT
L34         7657 SEA FILE=MEDLINE ABB=ON  SOCIAL ISOLATION+NT/CT
L35           60 SEA FILE=MEDLINE ABB=ON  SLEEP DISORDERS, CIRCADIAN RHYTHM+NT/C
                 T
L36          102 SEA FILE=MEDLINE ABB=ON  ELIMINATIVE BEHAVIOR, ANIMAL/CT
L45         4201 SEA FILE=MEDLINE ABB=ON  L26(L)(PD OR AD OR TU)/CT
L46        18033 SEA FILE=MEDLINE ABB=ON  ((L28 OR L29 OR L30 OR L31 OR L32 OR
                 L33 OR L34 OR L35 OR L36))(L)(DT OR PC)/CT
L49         2143 SEA FILE=MEDLINE ABB=ON  L45/MAJ
L71           20 SEA FILE=MEDLINE ABB=ON  L45 AND (L30 OR L32 OR L33)
L72           10 SEA FILE=MEDLINE ABB=ON  (L46 OR L49) AND L71


=> s l44 or l57 or l58 or l67 or l72; fil embase; d que l92; fil agricola caba biosis; d
que l128; d que l118; s l118 or l128; fil wpids; d que l152; d que l153; d que l160

L161        18 L44 OR L57 OR L58 OR L67 OR L72


FILE 'EMBASE' ENTERED AT 16:19:51 ON 20 MAR 2001
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 FILE COVERS 1974 TO 16 Mar 2001 (20010316/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

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L73        29260 SEA FILE=EMBASE ABB=ON  CHOLINESTERASE INHIBITOR+NT/CT
L74         9678 SEA FILE=EMBASE ABB=ON  COGNITIVE DEFECT/CT
L75        68057 SEA FILE=EMBASE ABB=ON  DEPRESSION/CT
L76        33950 SEA FILE=EMBASE ABB=ON  SLEEP DISORDER+NT/CT OR SLEEP WAKING
                 CYCLE/CT
L77        34500 SEA FILE=EMBASE ABB=ON  MEMORY+NT/CT
L78         4825 SEA FILE=EMBASE ABB=ON  CONFUSION/CT
L79       166525 SEA FILE=EMBASE ABB=ON  SOCIAL BEHAVIOR+NT/CT
L80         1004 SEA FILE=EMBASE ABB=ON  NOOTROPIC AGENT/CT
L81         8362 SEA FILE=EMBASE ABB=ON  AMNESIA/CT
L82         1721 SEA FILE=EMBASE ABB=ON  DEFECATION/CT
L83         6351 SEA FILE=EMBASE ABB=ON  MICTURITION/CT
L85        12026 SEA FILE=EMBASE ABB=ON  COMPANION ANIMAL# OR PET OR PETS
L86         6394 SEA FILE=EMBASE ABB=ON  ANIMAL BEHAVIOR/CT
L88        13417 SEA FILE=EMBASE ABB=ON  ACET!LCHOLINESTERASE#
L91       174541 SEA FILE=EMBASE ABB=ON  CAT/CT OR DOG/CT
L92            9 SEA FILE=EMBASE ABB=ON  L73 AND ((L74 OR L75 OR L76 OR L77 OR
                 L78 OR L79 OR L80 OR L81 OR L82 OR L83)) AND (L86 OR L85 OR
                 L91) AND L88


FILE 'AGRICOLA' ENTERED AT 16:19:54 ON 20 MAR 2001

FILE 'CABA' ENTERED AT 16:19:54 ON 20 MAR 2001
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FILE 'BIOSIS' ENTERED AT 16:19:54 ON 20 MAR 2001
                    Searched by Barb O'Bryen, STIC 308-4291
```

```
L98         3696 SEA ACET!LCHOLINESTERASE#(2A) INHIBIT?
L99         3394 SEA COGNITI?(2A)(DEFECT# OR DISORDER# OR DYSFUNCTION?)
L100      104600 SEA DEPRESSION
L102       62963 SEA MEMORY OR AMNESIA
L121      492516 SEA DOG# OR CAT# OR (PET OR COMPANION)(W) ANIMAL# OR PETS
L124      336627 SEA ?RESPIRATORY
L125        4702 SEA CARDIORESPIRATORY
L126        2730 SEA (L124 OR L125)(W) L100
L127      101870 SEA L100 NOT L126
L128           2 SEA L98 AND (L102 OR L127 OR L99) AND L121



L98         3696 SEA ACET!LCHOLINESTERASE#(2A) INHIBIT?
L101        2515 SEA COGNITIVE PROCESS?
L103       23589 SEA DISORIENT? OR CONFUS?
L104       14561 SEA SOCIAL?(2A)(INTERACT? OR BEHAVIOR#)
L105        4821 SEA SLEEP WAKE OR SLEEP(2A)(DISORDER#)
L106         337 SEA ELIMINAT?(2A)(INAPPROPRIAT? OR BEHAVIOR#)
L118          13 SEA L98 AND (L101 OR (L103 OR L104 OR L105 OR L106))



L162          15 L118 OR L128


FILE 'WPIDS' ENTERED AT 16:19:55 ON 20 MAR 2001
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FILE LAST UPDATED: 17 MAR 2001              <20010317/UP>
>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK            200115   <200115/DW>
DERWENT WEEK FOR CHEMICAL CODING:   200115
DERWENT WEEK FOR POLYMER INDEXING:  200115
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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                                              SEE HELP COST <<<

>>> FOR UP-TO-DATE INFORMATION ABOUT THE DERWENT CHEMISTRY
    RESOURCE, PLEASE VISIT
         http://www.derwent.com/chemistryresource/index.html <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/covcodes.html  <<<


L129         172 SEA FILE=WPIDS ABB=ON  ACET!LCHOLINESTERASE#(2A)INHIBIT?
L132          31 SEA FILE=WPIDS ABB=ON  COGNITIVE PROCESS?
L134          36 SEA FILE=WPIDS ABB=ON  SOCIAL?(2A)(INTERACT? OR BEHAVIOR#)
L136          24 SEA FILE=WPIDS ABB=ON  (DEFECAT? OR MICTUR? OR URINAT? OR
                 ELIMINAT?)(2A)(INAPPROPRIAT? OR BEHAVIOR#)
L138         110 SEA FILE=WPIDS ABB=ON  (ACET!LCHOLINE OR (ACET!L(W)( CHOLINE
                 OR THIOCHOLINE) OR ACET!LTHIOCHOLINE))(W)(ESTERASE# OR
                 ACETYLHYDROLASE OR (ACETYL HYDROLASE) OR HYDROLASE)
L139          74 SEA FILE=WPIDS ABB=ON  L138(2A) INHIBIT?
L151         559 SEA FILE=WPIDS ABB=ON  AGE RELATED
L152           3 SEA FILE=WPIDS ABB=ON  (L129 OR L139) AND (L132 OR L134 OR
                 L136 OR L151)
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Searched by Barb O'Bryen, STIC 308-4291

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L129        172 SEA FILE=WPIDS ABB=ON  ACET!LCHOLINESTERASE#(2A)INHIBIT?
L138        110 SEA FILE=WPIDS ABB=ON  (ACET!LCHOLINE OR (ACET!L(W)( CHOLINE
                OR THIOCHOLINE) OR ACET!LTHIOCHOLINE))(W)(ESTERASE# OR
                ACETYLHYDROLASE OR (ACETYL HYDROLASE) OR HYDROLASE)
L139         74 SEA FILE=WPIDS ABB=ON  L138(2A) INHIBIT?
L150      25488 SEA FILE=WPIDS ABB=ON  DOG# OR CAT# OR (PET OR COMPANION)(A)
                ANIMAL# OR PETS
L153          2 SEA FILE=WPIDS ABB=ON  (L129 OR L139) AND L150



L129        172 SEA FILE=WPIDS ABB=ON  ACET!LCHOLINESTERASE#(2A)INHIBIT?
L130        878 SEA FILE=WPIDS ABB=ON  COGNITI?(2A)(DEFECT# OR DISORDER# OR
                DYSFUNCTION?)
L131     331705 SEA FILE=WPIDS ABB=ON  MEMORY OR AMNESIA
L133       3908 SEA FILE=WPIDS ABB=ON  DISORIENT? OR CONFUS?
L135       1096 SEA FILE=WPIDS ABB=ON  SLEEP WAKE OR SLEEP(2A)(DISORDER# OR
                DISTURBANCE#)
L137      22686 SEA FILE=WPIDS ABB=ON  DEPRESSION
L138        110 SEA FILE=WPIDS ABB=ON  (ACET!LCHOLINE OR (ACET!L(W)( CHOLINE
                OR THIOCHOLINE) OR ACET!LTHIOCHOLINE))(W)(ESTERASE# OR
                ACETYLHYDROLASE OR (ACETYL HYDROLASE) OR HYDROLASE)
L139         74 SEA FILE=WPIDS ABB=ON  L138(2A) INHIBIT?
L158      87246 SEA FILE=WPIDS ABB=ON  ANIMAL#
L160          6 SEA FILE=WPIDS ABB=ON  (L129 OR L139) AND L158 AND (L130 OR
                L131 OR L133 OR L135 OR L137)


=> s l152 or l153 or l160

L163          8 L152 OR L153 OR L160

=> dup rem l161,l162,l24,l92,l163

FILE 'MEDLINE' ENTERED AT 16:20:39 ON 20 MAR 2001

FILE 'CABA' ENTERED AT 16:20:39 ON 20 MAR 2001
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FILE 'WPIDS' ENTERED AT 16:20:39 ON 20 MAR 2001
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PROCESSING COMPLETED FOR L161
PROCESSING COMPLETED FOR L162
PROCESSING COMPLETED FOR L24
PROCESSING COMPLETED FOR L92
PROCESSING COMPLETED FOR L163
L164         71 DUP REM L161 L162 L24 L92 L163 (1 DUPLICATE REMOVED)
                ANSWERS '1-18' FROM FILE MEDLINE
                          Searched by Barb O'Bryen, STIC 308-4291
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ANSWER '19' FROM FILE CABA
ANSWERS '20-32' FROM FILE BIOSIS
ANSWERS '33-54' FROM FILE CAPLUS
ANSWERS '55-63' FROM FILE EMBASE
ANSWERS '64-71' FROM FILE WPIDS

=> d ibib ab hitrn l164 1-71

L164 ANSWER 1 OF 71 MEDLINE
ACCESSION NUMBER: 2000396170 MEDLINE
DOCUMENT NUMBER: 20364616
TITLE: [Chief psychiatric problems in old age].
Die kardinalen psychiatrischen Probleme im Alter.
AUTHOR: Stoppe G
CORPORATE SOURCE: Klinik und Poliklinik fur Psychiatrie, Georg-August-Universitat Gottingen.. gstoppe@gwdg.de
SOURCE: INTERNIST, (2000 Jun) 41 (6) 538-43. Ref: 42
Journal code: GVX. ISSN: 0020-9554.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY WEEK: 20001003

L164 ANSWER 2 OF 71 MEDLINE
ACCESSION NUMBER: 2000200058 MEDLINE
DOCUMENT NUMBER: 20200058
TITLE: A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning.
AUTHOR: Burns M J; Linden C H; Graudins A; Brown R M; Fletcher K E
CORPORATE SOURCE: Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.. mburns@caregroup.harvard.edu
SOURCE: ANNALS OF EMERGENCY MEDICINE, (2000 Apr) 35 (4) 374-81.
Journal code: 4Z7. ISSN: 0196-0644.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY WEEK: 20000605
AB STUDY OBJECTIVE: To compare the efficacy and safety of physostigmine with benzodiazepines for the treatment of agitation and delirium associated with anticholinergic poisoning. METHODS: We conducted a retrospective study of 52 consecutive patients referred to a university hospital toxicology consultation service who were treated with physostigmine, benzo-diazepines, or both for anticholinergic agitation and delirium. Patients treated with physostigmine were compared with those treated with benzodiazepines with respect to demographics, severity of poisoning, response to treatment, side effects of treatment, and complications. RESULTS: Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively. Benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. Initial treatment with physostigmine (n=30) resulted in a significant decrease in the incidence of agitation (P <.001) and level of central nervous system stimulation (P <.001), whereas initial treatment with benzodiazepines (n=22) did not (P =.03 and P =.05, respectively). Patients treated initially with physostigmine had a significantly lower incidence of

complications (7% versus 46%; P <. 002) and a shorter time to recovery (median, 12 versus 24 hours; P =. 004) than those treated initially with benzodiazepines. There were no significant differences between these groups in the incidence of side effects (7% versus 14%; P =0.6) and length of stay (median, 32 versus 39 hours; P =.15). CONCLUSION: Results suggest that physostigmine is more effective and safer than benzodiazepines for the treatment of anticholinergic agitation and delirium. A prospective controlled study is necessary to confirm such findings.

L164 ANSWER 3 OF 71 MEDLINE
ACCESSION NUMBER: 2000492004 MEDLINE
DOCUMENT NUMBER: 20306910
TITLE: Clinical issues in current drug therapy for dementia.
AUTHOR: Forstl H
CORPORATE SOURCE: Department of Psychiatry and Psychotherapy, Technical University Munich, Germany.
SOURCE: ALZHEIMER DISEASE AND ASSOCIATED DISORDERS, (2000) 14 Suppl 1 S103-8.
Journal code: ALZ. ISSN: 0893-0341.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY WEEK: 20001204
AB Dementia resulting from Alzheimer disease is one of the most prevalent medical problems. Elaborate expert guidelines for the diagnosis and treatment of Alzheimer disease do not always take sufficient account of the resources available in general practice. The focus on pure Alzheimer disease can be inappropriate for the large proportion of mixed dementia cases in old age. Because of such guidelines, treatment with modern and effective drugs is often delayed until conservative dementia criteria are satisfied. Criteria for the discontinuation of antidementia drugs are highly questionable. Antidementia drug sales in Germany demonstrate that the majority of prescribers hold on to conservative attitudes and prefer Ginkgo biloba and memantine to acetylcholinesterase inhibitors. Disappointment after exaggerated expectations and financial restrictions in the health care sector may aggravate current underprescribing of antidementia drugs. Even though contemporary symptomatic treatments for Alzheimer disease are unsatisfactory, modern medicine has been very successful in the early diagnosis and treatment of other potential causes of dementia. Future strategies will include models for the early identification of individuals carrying a high risk of developing cognitive impairment during their lifetime.

L164 ANSWER 4 OF 71 MEDLINE
ACCESSION NUMBER: 2000037749 MEDLINE
DOCUMENT NUMBER: 20037749
TITLE: Treatment of Alzheimer's disease [see comments].
COMMENT: Comment in: N Engl J Med 2000 Mar 16;342(11):821; discussion 821-2
AUTHOR: Mayeux R; Sano M
CORPORATE SOURCE: Taub Institute on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.. rpm2@columbia.edu
CONTRACT NUMBER: AG07232 (NIA)
AG08702 (NIA)
AG10963 (NIA)
+
SOURCE: NEW ENGLAND JOURNAL OF MEDICINE, (1999 Nov 25) 341 (22) 1670-9. Ref: 111
Searched by Barb O'Bryen, STIC 308-4291

Journal code: NOW. ISSN: 0028-4793.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 200002

L164 ANSWER 5 OF 71 MEDLINE
ACCESSION NUMBER: 2000015880 MEDLINE
DOCUMENT NUMBER: 20015880
TITLE: Donepezil for psychotropic-induced memory loss.
AUTHOR: Jacobsen F M; Comas-Diaz L
CORPORATE SOURCE: Transcultural Mental Health Institute and the Department of Psychiatry and Behavioral Services, George Washington University School of Medicine, Washington, DC 20036-6043, USA.
SOURCE: JOURNAL OF CLINICAL PSYCHIATRY, (1999 Oct) 60 (10) 698-704.
Journal code: HIC. ISSN: 0160-6689.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104
AB BACKGROUND: Donepezil is an acetylcholinesterase inhibitor marketed for treatment of memory loss and behavioral deterioration associated with the acetylcholine deficit of Alzheimer's disease. We investigated the utility and tolerability of donepezil in nongeriatric affective illness for treatment of psychotropic-induced memory loss, dry mouth, and constipation. METHOD: Nondemented outpatients with stabilized DSM-IV affective illness took 5 mg/day of donepezil for 3 weeks and then increased to 10 mg/day in open trials. Self-rating scales of target symptoms were completed by patients before and 3 to 4 weeks after starting each dose condition. Patients who chose to continue donepezil therapy returned for clinical monitoring every 4 to 8 weeks. RESULTS: Eleven women and 11 men (mean +/- SD age = 45.4+/-8.5 years) completed donepezil trials. Nineteen patients with memory loss rated improvement while taking 5 mg/day of donepezil ($p<.001$); subsequently, 6 rated further improvement with 10 mg/day ($p = .057$). Donepezil, 5 mg/day, also reduced ratings of dry mouth ($N = 16$; $p<.001$) and constipation ($N = 11$; $p<.05$). Side effects included insomnia, nausea, vomiting, and diarrhea; surprisingly, 2 bipolar patients became manic within hours of starting donepezil. Sixteen patients (72%) continued donepezil for an average of 7 months. Consideration of family histories suggested that donepezil response in affective illness may be an early indicator of vulnerability to dementia of the Alzheimer's type. CONCLUSION: (1) Donepezil can reduce memory loss, dry mouth, and constipation in nongeriatric affective patients, but may trigger mania; and (2) long-term follow-up will reveal the predictive value for dementia of donepezil's memory restoration in nongeriatric subjects.

L164 ANSWER 6 OF 71 MEDLINE
ACCESSION NUMBER: 1999271541 MEDLINE
DOCUMENT NUMBER: 99271541
TITLE: Initiating and monitoring cholinesterase inhibitor treatment for Alzheimer's disease.
AUTHOR: Swanwick G R; Lawlor B A
CORPORATE SOURCE: Mercer's Institute for Research on Ageing and Eastern Health Board, Ireland.

Searched by Barb O'Bryen, STIC 308-4291

SOURCE: INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY, (1999 Apr) 14 (4) 244-8.
Journal code: CO0. ISSN: 0885-6230.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990902
AB The availability of acetylcholinesterase inhibitors for the treatment of Alzheimer's disease raises a number of clinical and ethical questions. Many of the guidelines published in an attempt to tackle these questions lack either clinical or scientific validity. Against this background a model is proposed whereby specialist monitoring using formal tests is neither appropriate nor necessary to determine whether an individual patient should continue or stop treatment. Instead the primary care physician should refer potentially suitable patients for specialist assessment to confirm the diagnosis/He/she should then initiate, monitor, and discontinue treatment based on the establishment of realistic treatment goals agreed with the patient/carer at the outset.

L164 ANSWER 7 OF 71 MEDLINE
ACCESSION NUMBER: 1999071558 MEDLINE
DOCUMENT NUMBER: 99071558
TITLE: [Drug therapy strategies in Alzheimer's disease]. Strategies des traitements medicamenteux de la maladie d'Alzheimer.
AUTHOR: Lacomblez L
CORPORATE SOURCE: Departements de neurologie et pharmacologie, Hopital La Pitie-La Salpetriere, Paris.
SOURCE: REVUE DU PRATICIEN, (1998 Nov 1) 48 (17) 1913-7.
Journal code: T1D. ISSN: 0035-2640.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
ENTRY MONTH: 199903
ENTRY WEEK: 19990301
AB Treatments in Alzheimer's disease include treatment of cognitive impairment and behavioral manifestations (agitation, depression, anxiety, delusions). It should be noted that many non-cognitive behaviors may have some relations to underlying cognitive impairment. In the not too distant future, physicians can expect to see a variety of medications and controversies over the benefits of slowing symptoms with cholinergic therapeutics approved for clinical use and (or) preventing progression of Alzheimer's disease assessed in clinical trials will emerge.

L164 ANSWER 8 OF 71 MEDLINE
ACCESSION NUMBER: 1999110026 MEDLINE
DOCUMENT NUMBER: 99110026
TITLE: Donepezil improves symptoms of delirium in dementia: implications for future research.
AUTHOR: Wengel S P; Roccaforte W H; Burke W J
CORPORATE SOURCE: Department of Psychiatry, University of Nebraska Medical Center, Omaha 68198-5575, USA.
SOURCE: JOURNAL OF GERIATRIC PSYCHIATRY AND NEUROLOGY, (1998 Fall) 11 (3) 159-61.
Journal code: AD5. ISSN: 0891-9887.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905

Searched by Barb O'Bryen, STIC 308-4291

ENTRY WEEK: 19990504
AB Delirium is a common complication of dementia and may produce considerable morbidity. In addition to psychotic symptoms such as hallucinations and delusions, delirium may produce considerable agitation, which may be refractory to conventional medications such as antipsychotics and benzodiazepines. The main approach to delirium is to treat any underlying medical problem that could cause the delirium. However, delirium is not always reversible, and there is no specific treatment for persistent delirium. The authors present a case of delirium complicating a preexisting dementia that resolved rapidly following initiation of the cholinesterase inhibitor donepezil, suggesting that cholinergic dysfunction may have played a role in the etiology of this patient's delirium. Future research needs to be directed at the issue of cholinergic activity in delirium through monitoring of serum anticholinergic activity and its response to procholinergic therapy.

L164 ANSWER 9 OF 71 MEDLINE
ACCESSION NUMBER: 1998260805 MEDLINE
DOCUMENT NUMBER: 98260805
TITLE: The fear of forgetfulness: a grassroots approach to an ethics of Alzheimer's disease [see comments].
COMMENT: Comment in: J Clin Ethics 1998 Spring;9(1):3-11.
AUTHOR: Post S G
CORPORATE SOURCE: Center for Biomedical Ethics, Case Western Reserve University, Cleveland, OH, USA.
SOURCE: JOURNAL OF CLINICAL ETHICS, (1998 Spring) 9 (1) 71-80.
Ref: 47
Journal code: A9M. ISSN: 1046-7890.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY WEEK: 19981001

L164 ANSWER 10 OF 71 MEDLINE
ACCESSION NUMBER: 97002107 MEDLINE
DOCUMENT NUMBER: 97002107
TITLE: Cholinergic delirium and neurotoxicity associated with tacrine for Alzheimer's dementia.
AUTHOR: Trzepacz P T; Ho V; Mallavarapu H
CORPORATE SOURCE: University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, PA 15213, USA.
SOURCE: PSYCHOSOMATICS, (1996 May-Jun) 37 (3) 299-301.
Journal code: QH4. ISSN: 0033-3182.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
ENTRY MONTH: 199704

L164 ANSWER 11 OF 71 MEDLINE
ACCESSION NUMBER: 96113703 MEDLINE
DOCUMENT NUMBER: 96113703
TITLE: Protracted post-traumatic confusional state treated with physostigmine.
AUTHOR: Eames P; Sutton A
CORPORATE SOURCE: Grafton Manor Brain Injury Rehabilitation Unit, Northants, UK.
SOURCE: BRAIN INJURY, (1995 Oct) 9 (7) 729-34.
Journal code: BRA. ISSN: 0269-9052.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
AB A case study is presented of confusion in a head-injured man, lasting for more than 2 years, when intermittent treatment with physostigmine resulted in progressive improvement in both confusion and usable cognitive functions. Aetiological mechanisms and implications for treatment plans are discussed.

L164 ANSWER 12 OF 71 MEDLINE
ACCESSION NUMBER: 89030960 MEDLINE
DOCUMENT NUMBER: 89030960
TITLE: Chronic treatment with cholinesterase inhibitors increases alpha 2-adrenoceptors in rat brain.
AUTHOR: Hollingsworth P J
CORPORATE SOURCE: Department of Pharmacology, University of Michigan Medical School, Ann Arbor 48109.
CONTRACT NUMBER: ES-03490 (NIEHS)
MH-36226 (NIMH)
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1988 Aug 24) 153 (2-3) 167-73.
Journal code: EN6. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198902
AB The specific binding of [3H]clonidine to alpha 2-adrenoceptors on neural membranes isolated from various brain areas was determined with rats treated for 7-14 days with the cholinesterase inhibitors neostigmine, triorthocresyl phosphate (TOCP), diisopropylfluorophosphate (DFP) and paraoxon, or with vehicle. Treatment with all four inhibitors increased the number of clonidine binding sites in various brain areas. In those areas which demonstrated significant increases in [3H]clonidine binding, there was also a significant inhibition of acetylcholinesterase activity. The possibility is discussed that increases in brain alpha 2-adrenoceptors are related to the alterations in mood seen in individuals chronically exposed to organophosphorus cholinesterase inhibitors.

L164 ANSWER 13 OF 71 MEDLINE
ACCESSION NUMBER: 86284021 MEDLINE
DOCUMENT NUMBER: 86284021
TITLE: Actions of cimetidine and ranitidine at some cholinergic sites: implications in toxicology and anesthesia.
AUTHOR: Gwee M C; Cheah L S
SOURCE: LIFE SCIENCES, (1986 Aug 4) 39 (5) 383-8. Ref: 51
Journal code: L62. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198611
AB Cimetidine and ranitidine are specific and potent H2-receptor antagonists widely used in the effective therapy of peptic ulcer disease. The drugs also possess other pharmacological properties unrelated to H2-receptor antagonism. More recently large experimental doses of cimetidine or ranitidine were found to have anticholinesterase, ganglion blocking and neuromuscular blocking activities. Actions of the drugs at such cholinergic sites may account for some of their clinically documented

adverse effects. The toxicological implications of these findings including the potential for drug interactions to occur, especially during some anesthetic procedures, are discussed.

L164 ANSWER 14 OF 71 MEDLINE
ACCESSION NUMBER: 86231385 MEDLINE
DOCUMENT NUMBER: 86231385
TITLE: Drugs as research tools in psychology: cholinergic drugs and aggression.
AUTHOR: Bell R; Warburton D M; Brown K
SOURCE: NEUROPSYCHOBIOLOGY, (1985) 14 (4) 181-92. Ref: 84
Journal code: NZM. ISSN: 0302-282X.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
AB A review of studies using cholinergic drugs as tools to investigate the neural mechanisms mediating affective and predatory aggressive behaviour reveals that the same two cholinergic systems are involved with both sorts of behaviour. There is a brain muscarinic system initiating aggression and a nicotinic system which inhibits aggressive behaviour. This evidence suggests that there could be two possible forms of cholinergic therapy for aggression, cholinolytics and nicotinic agonists. These possibilities are discussed.

L164 ANSWER 15 OF 71 MEDLINE
ACCESSION NUMBER: 86052067 MEDLINE
DOCUMENT NUMBER: 86052067
TITLE: Drug treatment of bipolar depression and mania.
AUTHOR: Cookson J C
SOURCE: BRITISH JOURNAL OF HOSPITAL MEDICINE, (1985 Sep) 34 (3) 172-5. Ref: 92
Journal code: BZ5. ISSN: 0007-1064.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
AB Bipolar manic-depressive disorder may present as mania, depression, or mixed states, and there is increasing knowledge of its responsiveness to drugs as therapeutic agents. In addition a number of drugs may act as aggravating factors for the disorder.

L164 ANSWER 16 OF 71 MEDLINE
ACCESSION NUMBER: 84039559 MEDLINE
DOCUMENT NUMBER: 84039559
TITLE: [Ambulatory treatment of depressions without tranquilizers].
Ambulante Behandlung von Depressionen ohne Tranquilizer.
AUTHOR: Ikonomoff S I
SOURCE: MMW. MUNCHENER MEDIZINISCHE WOCHENSCHRIFT, (1983 Sep 2) 125 (35) 749-50.
Journal code: NMM. ISSN: 0341-3098.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
ENTRY MONTH: 198402

L164 ANSWER 17 OF 71 MEDLINE

ACCESSION NUMBER: 78202353 MEDLINE
DOCUMENT NUMBER: 78202353
TITLE: The prevention of postanesthetic delirium.
AUTHOR: Savage G J; Metzger J T
SOURCE: PLASTIC AND RECONSTRUCTIVE SURGERY, (1978 Jul) 62 (1) 81-4.
Journal code: P9S. ISSN: 0032-1052.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197810
AB We recommend the use of one dose of physostigmine salicylate, a few minutes before the termination of a general anesthetic, to prevent confusion, struggling, disorientation, or delirium during the recovery from anesthesia. We believe that it is well to prevent such behavior, particularly in patients who have just undergone reconstructive surgery where the unmanageable behavior could jeopardize surgical results. Our results indicate that such behavior is largely preventable.

L164 ANSWER 18 OF 71 MEDLINE
ACCESSION NUMBER: 77135881 MEDLINE
DOCUMENT NUMBER: 77135881
TITLE: When does inhibition of brain acetylcholinesterase cause amnesia in rats?.
AUTHOR: George G; Mellanby H; Mellanby J
SOURCE: BRAIN RESEARCH, (1977 Feb 25) 122 (3) 568-74.
Journal code: B5L. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197707

L164 ANSWER 19 OF 71 CABA COPYRIGHT 2001 CABI DUPLICATE 1
ACCESSION NUMBER: 89:22350 CABA
DOCUMENT NUMBER: 890593771
TITLE: Spatial memory impairment and central muscarinic receptor loss following prolonged treatment with organophosphates
AUTHOR: McDonald, B. E.; Costa, L. G.; Murphy, S. D.
CORPORATE SOURCE: Dep. Environmental Health, SC-34, Univ. Washington, Seattle, WA 98195, USA.
SOURCE: Toxicology Letters, (1988) Vol. 40, No. 1, pp. 47-56. 38 ref.
ISSN: 0378-4274
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Memory impairment is one of the recurrent complaints of agricultural workers repeatedly exposed to organophosphorus insecticides. In an effort to establish an animal model for such behavioural effects, which would allow study of its underlying biochemical mechanism(s), spatial memory (SM) was evaluated in animals following repeated organophosphate (OP) exposure. Male Long-Evans rats were given daily i.p. injections of either diisopropylfluorophosphate (DFP; 1 mg/kg/day) or disulfoton (2 mg/kg/day) for 14 days. **Acetylcholinesterase** activity was **inhibited** 71-77% in the cortex, hippocampus and striatum of rats treated with DFP, and 73-74% in those treated with disulfoton. Binding of [3H]quinuclidinyl benzilate to cholinergic muscarinic receptors in the same areas was reduced 16-28% in OP-treated rats. This decrease was due to a reduction in muscarinic receptor density (Bmax), with no changes in receptor affinity. At the end of the treatment, rats were tested for SM using the spontaneous alternation (SA) task in a T-maze. Rates of true SA were 64.4, 45.0 and

44.8% in animals which received corn oil, DFP or disulfoton, respectively ($P < 0.05$). These results indicate that prolonged **inhibition** of **acetylcholinesterase** caused by repeated OP exposure alters SM functions in rats, as well as causing a loss of muscarinic receptors. Considering the role of the cholinergic system in **cognitive processes**, these biochemical alterations could be related to the observed behavioural changes and may offer a potential explanation of the memory impairment reported by workers chronically exposed to OPs.

L164 ANSWER 20 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:91188 BIOSIS
DOCUMENT NUMBER: PREV200100091188
TITLE: Fulminant chemical hepatitis possibly associated with donepezil and sertraline therapy.
AUTHOR(S): Verrico, Margaret M. (1); Nace, David A.; Towers, Adele L.
CORPORATE SOURCE: (1) Drug Information and Pharmacoepidemiology Ctr., 137 Victoria Hall, Pittsburgh, PA, 15261 USA
SOURCE: Journal of the American Geriatrics Society, (December, 2000) Vol. 48, No. 12, pp. 1659-1663. print.
ISSN: 0002-8614.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB OBJECTIVE: To describe a case of fulminant hepatitis possibly related to concomitant donepezil and seratriline therapy. PATIENT AND SETTING: An 83-year-old woman treated in a dementia care facility and later in a tertiary medical center. INTERVENTION AND MANAGEMENT: Discontinuation of donepezil and sertraline therapy with subsequent improvement evidenced by liver biopsy and liver function tests. RESULTS: An older woman with Alzheimer's disease was admitted to a dementia care facility because of aggressive behavior. Treatment with sertraline was initiated in February 1998. Sertraline doses were increased gradually to 200 mg daily by May 1998, and some improvement in behavior was seen. Concomitant therapy with donepezil 5 mg qhs was initiated June 26, 1998. Ten days later, **confusion** and jaundice were noted. Total bilirubin was 5.6 mg/dL, GGTP was 1208 IU/L, and alkaline phosphatase was 369 IU/L. Computed tomography revealed cholelithiasis without ductal dilation. Liver, spleen, and pancreas seemed normal. Donepezil and sertraline were discontinued. The patient was admitted to our institution and treated for dehydration. A liver biopsy revealed scattered portal eosinophils and prominent cholestasis consistent with acute chemical hepatitis. The GGTP and total bilirubin of this patient peaked at 2235 IU/L and 22.6 mg/dL, respectively. The patient improved, and her liver function tests normalized over the next 2 months.

L164 ANSWER 21 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:474506 BIOSIS
DOCUMENT NUMBER: PREV200000474506
TITLE: Treatment of REM **sleep** behavior **disorder** with donepezil: A report of three cases.
AUTHOR(S): Ringman, J. M.; Simmons, J. H. (1)
CORPORATE SOURCE: (1) Sadler Clinic Sleep Disorder Center, 9201 Pinecroft Drive, The Woodlands, TX, 77380 USA
SOURCE: Neurology, (September 26, 2000) Vol. 55, No. 6, pp. 870-871. print.
ISSN: 0028-3878.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Three patients with REM behavior disorder whose nocturnal symptoms were markedly improved by treatment with the **acetylcholinesterase** **inhibitor** donepezil are reported. Donepezil may have a role in the

treatment of REM behavior disorder, possibly through its actions on cholinergic pathways in the brainstem.

L164 ANSWER 22 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:79338 BIOSIS
DOCUMENT NUMBER: PREV200100079338
TITLE: Intoxication with huperzine A, a potent anticholinesterase found in the fir club moss.
AUTHOR(S): Felgenhauer, Norbert (1); Zilker, Thomas; Worek, Franz; Eyer, Peter
CORPORATE SOURCE: (1) Toxikologische Abteilung der II. Med. Klinik, Klinikum r.d. Isar, TU Muenchen, Ismaninger Str. 22, 81675, Muenchen: N.Felgenhauer@lrz.tu-muenchen.de Germany
SOURCE: Journal of Toxicology Clinical Toxicology, (December, 2000) Vol. 38, No. 7, pp. 803-808. print.
ISSN: 0731-3810.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: Herbs from Lycopodium are generally reputed to be nontoxic and are occasionally used for preparing a salubrious tea. In Europe, the common Lycopodium clavatum can be easily **confused** with Lycopodium selago, the fir club moss. Case Report: We report 2 patients who drank a tea, erroneously prepared from dried herbs of Lycopodium selago, which resulted in sweating, vomiting, diarrhea, dizziness, cramps, and slurred speech. These symptoms were suggestive of a cholinergic mechanism. To elucidate the active principle, aqueous extracts of Lycopodium selago were checked for their suspected anticholinesterase activity using human erythrocytes as an enzyme source in a modified Ellman assay. The extracts did exhibit significant anticholinesterase activity. The anticholinesterase(s) were most effectively extracted with dichloromethane and isolated by high-performance liquid chromatography. The major compound with anticholinesterase activity co-chromatographed with authentic huperzine A, but had a 2-3-fold higher inhibitory potency than the racemic standard. The amount of huperzine A found in the Lycopodium selago sample used for the tea preparation was calculated to be sufficient for a relevant **acetylcholinesterase inhibition**. Conclusion: The signs and symptoms of Lycopodium selago poisoning are consistent with the anticholinesterase activity of huperzine A and should favorably respond to atropine therapy. This report demonstrates once more that laymen should not be encouraged to gather their remedies from "Mother Nature" without advanced botanical knowledge.

L164 ANSWER 23 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:148059 BIOSIS
DOCUMENT NUMBER: PREV199900148059
TITLE: Clinical profile of donepezil in the treatment of Alzheimer's disease.
AUTHOR(S): Doody, R. S. (1)
CORPORATE SOURCE: (1) Baylor Coll. Med., Dep. Neurology, 6550 Fannin, Ste 1801, Houston, TX 77030-3498 USA
SOURCE: Gerontology, (Jan., 1999) Vol. 45, No. SUPPL. 1, pp. 23-32.
ISSN: 0304-324X.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Although the underlying pathogenesis of Alzheimer's disease (AD) is not fully understood, one of its key features is the widespread loss of central cholinergic innervation, known to be fundamental for **cognitive processes**. This finding led to the hypothesis that pharmacological enhancement of acetylcholine (ACh) neurotransmission may alleviate the symptoms of AD. Currently, cholinergic therapy, particularly cholinesterase (ChE) inhibition, represents the most

realistic approach to the symptomatic treatment of AD. Donepezil HCl, for example, is a piperidine-based, reversible **acetylcholinesterase** (AChE) **inhibitor**, chemically distinct from other ChE inhibitors and rationally designed for the symptomatic treatment of AD. It is highly selective for centrally acting AChE, with little or no affinity for butyrylcholinesterase, present predominantly in the periphery. Phase I and II clinical trials demonstrated donepezil's favourable pharmacokinetic, pharmacodynamic and safety profile with no requirement for dose modification in the elderly or in patients with renal or hepatic impairment. Furthermore, its long half-life supports a simple and convenient once daily dosing regimen. Subsequent to encouraging phase II clinical trial results, two pivotal, randomized, doubleblind phase III trials (of 15 and 30 weeks' duration) demoonstrated highly significant improvements in cognition and global function in mild to moderately severe AD patients treated with either 5 or 10 mg/day donepezil compared with placebo. Adverse events in the phase II and III trials, primarily cholinergic in nature, were traneitn and generally mild in severity and resolved during continued donepezil administration. Thus, the donepezil clinical trials programme has shown that htis drug is a clinically effective and well-tolerated, once-daily treatment for the symptoms of mild to moderately severe AD.

L164 ANSWER 24 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:78255 BIOSIS
DOCUMENT NUMBER: PREV199900078255
TITLE: Pharmacologic strategies for augmenting cognitive performance in schizophrenia.
AUTHOR(S): Friedman, Joseph I. (1); Temporini, Humberto; Davis, Kenneth L.
CORPORATE SOURCE: (1) Mount Sinai Sch. Med., Dep. Psychiatry, Box 1230, One Gustave Levy Place, New York, NY 10029 USA
SOURCE: Biological Psychiatry, (Jan. 1, 1999) Vol. 45, No. 1, pp. 1-16.
ISSN: 0006-3223.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB There is recognition that the cognitive symptoms of schizophrenia have the most substantial impact on illness outcome. Domains of cognition reported to be significantly affected include serial learning, executive function, vigilance, and distractibility, to name a few. Dopamine activity at D1 receptors mediates many **cognitive processes** subserved by the prefrontal cortex (PFC), particularly working memory. The number of D1 receptors in the PFC is decreased in schizophrenics and is unaffected by chronic administration of typical neuroleptics. Therefore, medications that increase dopamine in the PFC, such as atypical neuroleptics, or that directly activate the D1 receptor may prove useful in the remediation of prefrontal-dependent cognitive deficits in schizophrenia. Decreased levels of cortical norepinephrine (NE) are associated with impaired learning and working memory in animal models, and can be reversed by drugs that restore NE activity. More specifically, alpha-2 adrenergic receptor agonists have been particularly effective in improving delayed response performance in young monkeys with localized 6-hydroxydopamine lesions in the PFC. Furthermore, human postmortem studies have demonstrated decreased NE in the frontal cortex of demented schizophrenic patients. Therefore, alpha-2 receptor agonists hold promise as drugs to improve cognitive performance on tasks dependent upon PFC function in schizophrenics. Finally, the finding that cortical choline acetyl transferase activity correlates with Clinical Dementia Rating scores in schizophrenic patients and that cholinomimetic drugs enhance cognition in healthy subjects suggests that cholinergic drugs may also treat cognitive symptoms in schizophrenia. Two potential types of cholinomimetics for use in schizophrenics are the **acetylcholinesterase inhibitors** and M1/M4 muscarinic

agonists, both of which increase cortical cholinergic activity.

L164 ANSWER 25 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:457426 BIOSIS
DOCUMENT NUMBER: PREV199799756629
TITLE: Pontine nitric oxide modulates acetylcholine release, rapid eye movement sleep generation, and respiratory rate.
AUTHOR(S): Leonard, Timothy O.; Lydic, Ralph (1)
CORPORATE SOURCE: (1) Dep. Anesthesia, Pennsylvania State Univ., Coll. Med., Hershey, PA 17033, USD
SOURCE: Journal of Neuroscience, (1997) Vol. 17, No. 2, pp. 774-785.
ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Pontine cholinergic neurotransmission is known to play a key role in the regulation of rapid eye movement (REM) sleep and to contribute to state-dependent respiratory depression. Nitric oxide (NO) has been shown to alter the release of acetylcholine (ACh) in a number of brain regions, and previous studies indicate that NO may participate in the modulation of **sleep/wake** states. The present investigation tested the hypothesis that inhibition of NO synthase (NOS) within the medial pontine reticular formation (mPRF) of the unanesthetized cat would decrease ACh release, inhibit REM sleep, and prevent cholinergically mediated respiratory depression. Local NOS inhibition by microdialysis delivery of NG-nitro-L-arginine (NLA) significantly reduced ACh release in the cholinergic cell body region of the pedunculopontine tegmental nucleus and in the cholino-ceptive mPRF. A second series of experiments demonstrated that mPRF microinjection of NLA significantly reduced the amount of REM sleep and the REM sleep-like state caused by mPRF injection of the **acetylcholinesterase inhibitor** neostigmine. Duration but not frequency of REM sleep epochs was significantly decreased by mPRF NLA administration. Injection of NLA into the mPRF before neostigmine injection also blocked the ability of neostigmine to decrease respiratory rate during the REM sleep-like state. Taken together, these findings suggest that mPRF NO contributes to the modulation of ACh release, REM sleep, and breathing.

L164 ANSWER 26 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:505567 BIOSIS
DOCUMENT NUMBER: PREV199799804770
TITLE: Tacrine response: Review of two years of prescription.
AUTHOR(S): Augry, F.; Darchy, A.; De Rotrou, J.; Guelfi, M. C. (1); Forette, F.
CORPORATE SOURCE: (1) Serv. Pharmacie, Hopital Broca, 54-56 rue Pascal, 75013 Paris France
SOURCE: Journal de Pharmacie Clinique, (1997) Vol. 16, No. 3, pp. 183-187.
ISSN: 0291-1981.
DOCUMENT TYPE: Article
LANGUAGE: French
SUMMARY LANGUAGE: French; English
AB Alzheimer's disease is a degenerative disease leading to dementia associated with anatomo-pathologic and neurochemical modifications which induce a deterioration of the cholinergic system. The main clinical signs are: cognitive distress, intellectual **confusion** and performance difficulties. Psychometric tests as MMSE (mini mental state examination) and Adas-Cog (cognitive function of Alzheimer's disease assessment scale) can evaluate the cognitive functions. Tacrine (Cognex) therapy **inhibits** the **acetylcholinesterase**. The treatments were: 40 mg daily of tacrine for 6 weeks, 80 mg/d next 6 weeks, 120 mg/d for 2 months and finally 160 mg/d. The aim of our work was to analyse the

response to tacrine and subsequent evolution of 131 out-patients being treated at the Broca hospital since the commercialisation of tacrine (October 1994). We compared the Adas-Cog scores after each dosage with those of the same test before treatment. The patients were divided into three groups according to the results: the responding group "R": decrease of 4 points or more between two scores, the stabilizing group "S" decrease of zero to 3 points between two scores, the non-responding group "N": increase between two scores. The percentage of "R" patients at each dose level were: 26% at 40 mg/d of tacrine, 38% at 80 mg/d, 52% at 120 mg/d and 34% at 160 mg/d. The side effects of tacrine which led to the patients stopping the treatment were gastro-intestinal diseases (11%), hepatic diseases (7%), performance troubles (3%) and cutaneous diseases (1.5%). Cognex improves the cognitive functions in patients with Alzheimer's disease and inhibits the evolution of the disease but does not stop it completely. Our study shows that 120 mg/d of tacrine is the optimal dosage with which to treat Alzheimer's disease.

L164 ANSWER 27 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:289029 BIOSIS
DOCUMENT NUMBER: PREV199699011385
TITLE: Alpha-2-Adrenoceptor antagonists potentiate **acetylcholinesterase inhibitor** effects on passive avoidance learning in the rat.
AUTHOR(S): Camacho, Fernando; Smith, Craig P.; Vargas, Hugo M.; Winslow, James T. (1)
CORPORATE SOURCE: (1) Neurosci. Ther. Domain, P.O. Box 2500, Rt. 202-206, Somerville, NJ 08876-1258 USA
SOURCE: Psychopharmacology, (1996) Vol. 124, No. 4, pp. 347-354. ISSN: 0033-3158.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The cholinergic hypothesis of Alzheimer's disease (AD) has strongly influenced research on learning and memory over the last decade. However, there has been limited success treating AD dementia with cholinomimetics. Furthermore, there are indications that other neurotransmitter systems affected by this disease may be involved in **cognitive processes**. Animal studies have suggested that norepinephrine and acetylcholine may interact in learning and memory. The current experiments investigate this interaction in a step-down passive avoidance paradigm after coadministration of **acetylcholinesterase inhibitors** and alpha-2-adrenoceptor antagonists. Administration of **acetylcholinesterase inhibitors** heptylphysostigmine (0.625-5.0 mg/kg, IP), tacrine (2.5-10.0 mg/kg, PO), velnacrine (0.312-2.5 mg/kg, SC), and galanthamine (0.312-2.5 mg/kg, IP) each enhanced retention of a passive avoidance response at selected moderate doses administered 30-60 min prior to training. The alpha-2 adrenoceptor antagonists idazoxan (0.312-2.5 mg/kg, IP), yohimbine (0.078-0.312 mg/kg, IP) and P86 7480 (0.156-0.625 mg/kg, IP) alone failed to enhance learning in this paradigm. Coadministration of a subthreshold dose of heptylphysostigmine (0.625 mg/kg, IP) with doses of idazoxan, yohimbine or P86 7480 enhanced passive avoidance learning. This synergistic interaction may represent effects of antagonism of presynaptic alpha-2-adrenoceptor since coadministration of heptylphysostigmine and the selective postsynaptic alpha-2-adrenoceptor antagonist SKF104856 did not result in enhanced learning. Taken together these data suggest noradrenergic activation through pre-synaptic alpha-2-adrenoceptor blockade may potentiate cholinergic activity in the formation of a long-term memory trace. These observations may have implications for the treatment of AD with cholinergic and adrenergic agents.

L164 ANSWER 28 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:122461 BIOSIS

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT NUMBER: BA93:68261
TITLE: REVERSAL OF ORPHENADRINE-INDUCED VENTRICULAR TACHYCARDIA WITH PHYSOSTIGMINE.
AUTHOR(S): DANZE L K; LANGDORF M I
CORPORATE SOURCE: UNIV. CALIF., IRVINE MED. CENT., DIV. EMERGENCY MED., 101 CITY DRIVE, ROUTE 128, ORANGE, CALIF. 92668.
SOURCE: J EMERG MED, (1991) 9 (6), 453-458.
CODEN: JEMMDO.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB A 3-year-old boy developed **confusion**, generalized tonic-clonic seizures, and sustained ventricular tachycardia following ingestion of an unknown quantity of orphenadrine (Norflex). Although refractory to precordial thump, synchronous cardioversion, and lidocaine, the ventricular tachycardia was reversed by intravenous administration of the tertiary **acetylcholinesterase inhibitor** physostigmine. We discuss the underlying physiology and manifestations of anticholinergic overdose, the specific manifestation of orphenadrine overdose, and the current recommendations regarding the utilization and toxicity of physostigmine in the treatment of anticholinergic syndromes and orphenadrine intoxication.

L164 ANSWER 29 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:438386 BIOSIS
DOCUMENT NUMBER: BA92:94551
TITLE: EFFECTS OF ACUTE ADMINISTRATION OF SOMAN ON SPINAL CORD REFLEXES IN THE **CAT**.
AUTHOR(S): GOLDSTEIN B D
CORPORATE SOURCE: DEP. PHARMACOL. TOXICOL., MED. COLL. GEORGIA, AUGUSTA, GA. 30912-2300, USA.
SOURCE: TOXICOL LETT (AMST), (1991) 57 (2), 139-146.
CODEN: TOLED5. ISSN: 0378-4274.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The acute effects of the organophosporus **acetylcholinesterase inhibitor**, soman, was studied on spinal cord reflexes in the spinal cord transected **cat**. It was found that doses of 10 .mu.g/kg significantly altered the monosynaptic and dorsal root reflexes by causing an initial **depression** lasting about 20 min followed by a later facilitation lasting over 3 h. A higher dose of soman (20 .mu.g/kg) caused the initial but did not produce the later facilitation. Cholinergic antagonists were used to determine whether the changes were related to **inhibition** of **acetylcholinesterase** or whether they were non-specific. It was found that mecamylamine blocked the **depression** and the facilitation while atropine depressed the spinal cord potentials. These data show that acute administration of 10.mu.mg/kg soman produces specific effects on spinal cord reflexes which could be characterized as resulting from **inhibition** of **acetylcholinesterase** similar to the carbamate inhibitor, physostigmine.

L164 ANSWER 30 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:279018 BIOSIS
DOCUMENT NUMBER: BA92:11633
TITLE: MECHANISMS OF RESPIRATORY FAILURE PRODUCED BY NEOSTIGMINE AND DFP.
AUTHOR(S): FLEMING N W; HENDERSON T R; DRETCHEN K L
CORPORATE SOURCE: DEP. ANESTHESIOLOGY, UNIV. CALIFORNIA DAVIS, SCH. MED., TB-170, DAVIS, CALIF. 95616.
SOURCE: EUR J PHARMACOL, (1991) 195 (1), 85-92.
CODEN: EJPHAZ. ISSN: 0014-2999.
FILE SEGMENT: BA; OLD

Searched by Barb O'Bryen, STIC 308-4291

LANGUAGE: English

AB **Acetylcholinesterase inhibitors** produce diverse physiologic effects, but lethal exposure consistently produces respiratory failure due to neuromuscular paralysis or **depression** of respiratory control centers in the medulla. Simultaneous measurement of gastrocnemius muscle contraction and efferent phrenic nerve activity was used to determine the primary cause of respiratory failure produced by neostigmine and diisopropyl fluorophosphate (DFP) in anesthetized **cats**. Both neostigmine and DFP abolished phrenic nerve activity prior to producing neuromuscular blockade. Furthermore, neostigmine did not alter brain acetylcholinesterase activity and pretreatment with either atropine methylbromide or atropine increased the dose of neostigmine required to abolish phrenic nerve activity. In contrast, DFP abolished brain cholinesterase activity and only atropine inhibited its respiratory effects. Despite the loss of efferent phrenic nerve activity, there is no evidence of a direct effect of neostigmine on respiratory control centers. Neostigmine may instead alter afferent inputs which modulate respiration to produce a reflex respiratory failure.

L164 ANSWER 31 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1987:244202 BIOSIS
DOCUMENT NUMBER: BR32:119460
TITLE: A COMPARISON OF THE CHOLINERGIC PROPERTIES OF FAMOTIDINE A NEW H-2 BLOCKER TO CIMETIDINE AND RANITIDINE.
AUTHOR(S): KOSH J W; CHAPMAN J M; SOWELL J W SR
CORPORATE SOURCE: COLLEGE OF PHARM., UNIV. S. CAROLINA, COLUMBIA, S.C. 29208.
SOURCE: 71ST ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, WASHINGTON, D.C., USA, MARCH 29-APRIL 2, 1987. FED PROC, (1987) 46 (3), 856.
CODEN: FEPRA7. ISSN: 0014-9446.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L164 ANSWER 32 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1981:295139 BIOSIS
DOCUMENT NUMBER: BA72:80123
TITLE: EVALUATION OF A NEW HOMOGENEOUS ENZYME INHIBITOR IMMUNOASSAY OF SERUM THYROXINE WITH USE OF A BI CHROMATIC ANALYZER.
AUTHOR(S): FINLEY P R; WILLIAMS R J; LICHTI D A
CORPORATE SOURCE: DEP. CLIN. PATHOL., UNIV. ARIZ. HEALTH SCI. CENT., TUCSON, ARIZ. 85724, USA
SOURCE: CLIN CHEM, (1980) 26 (12), 1723-1726.
CODEN: CLCHAU. ISSN: 0009-9147.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB A new homogeneous enzyme immunoassay of thyroxine with use of a discrete analyzer (the ABA-100 Bichromatic Analyzer), modified with an auxiliary dispenser assembly, was evaluated. The assay is based on inhibition of hydrolysis of the substrate, acetyl-(beta.-methylthio)choline iodide, by acetylcholinesterase (acetylcholine hydrolase; EC 3.1.1.7). Thyroxine covalently linked to a cholinesterase **inhibitor** irreversibly **inhibits acetylcholinesterase**, but if this thyroxine conjugate is bound to antibody it is not inhibitory. Seventy-five patients' samples may be analyzed in 1 h of instrument time. Precision and accuracy are excellent, results correlate well with those by radioimmunoassay, and there were no instances of **confused** clinical interpretation resulting from use of the proposed assay.

L164 ANSWER 33 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:782696 CAPLUS
Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT NUMBER: 133:344629
TITLE: Treatment of **age-related** behavioral disorders of pets with **acetylcholine esterase inhibitors**, and pharmaceutical compositions containing piperidines for the treatment
INVENTOR(S): Landi, Christine Mary
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000309545	A2	20001107	JP 2000-114594	20000417
EP 1050303	A2	20001108	EP 2000-303253	20000413
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			US 1999-131243	19990427

OTHER SOURCE(S): MARPAT 133:344629
AB **Age-related** behavioral disorders (e.g. cognition disorder, amnesia, melancholia, and **confusion**) are treated by administration of an ED of piperidines I [R1, R2 = H, C1-6 alkoxy, (un)substituted PhCH2O, halo, NO2, amino, (un)substituted pyridylmethoxy, (un)substituted thienylmethoxy, etc.; X = O, S; Y = (CH2)m, CH:CH(CH2)n, O(CH2)m, etc.; m = 1-3; n = 0-3; L = (un)substituted Ph, cinnamyl, pyridylmethyl, etc.; R7, R8 = H, C1-6 alkyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, etc.], their salts, or their solvates as acetylcholine esterase inhibitors. Icopezil is effect for treatment of such disorders.
IT **9000-81-1, Acetylcholine esterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of **age-related** behavioral disorders of pets with piperidines as **acetylcholine esterase inhibitors**)

L164 ANSWER 34 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:237803 CAPLUS
DOCUMENT NUMBER: 133:12667
TITLE: The effect of rivastigmine on sleep in elderly healthy subjects
AUTHOR(S): Schredl, M.; Weber, B.; Braus, D.; Heuser, I.
CORPORATE SOURCE: Central Institute of Mental Health, Mannheim, 68072, Germany
SOURCE: Exp. Gerontol. (2000), 35(2), 243-249
CODEN: EXGEAB; ISSN: 0531-5565
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous research has shown that acetylcholinesterase inhibitors may affect REM sleep, however, results are inconclusive. From the present findings it is concluded that the effects of rivastigmine, a reversible acetycholinesterase inhibitor, on REM sleep are more pronounced in the elderly where the authors found REM latency to be reduced. This may be explained by better bioavailability and/or by reduced stability of the circadian rhythmicity in elderly individuals. Because rivastigmine is used in the treatment of Alzheimer's disease, further research investigating the relationship between the REM enhancing properties of rivastigmine and cognitive functioning seems promising.
IT **9000-81-1, Acetylcholinesterase**
Searched by Barb O'Bryen, STIC 308-4291

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitor**; rivastigmine on sleep in elderly)

REFERENCE COUNT: 25
REFERENCE(S):
(1) Berkowitz, A; Psych Res 1990, V33, P113 CAPLUS
(5) Farlow, M; Am J Health System Pharm Suppl 1998, V55, PS5 CAPLUS
(6) Friess, E; Am J Physiol 1995, V268, PE107 CAPLUS
(9) Hohagen, F; Neuropsychopharmacology 1993, V9, P225 CAPLUS
(10) Holsboer-Trachsler, E; Neuropsychopharmacology 1993, V8, P87 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 35 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:458267 CAPLUS
DOCUMENT NUMBER: 133:172050
TITLE: Biochemical and neurobehavioral profile of CHF2819, a novel, orally active acetylcholinesterase inhibitor for Alzheimer's disease
AUTHOR(S): Trabace, Luigia; Cassano, Tommaso; Steardo, Luca; Pietra, Claudio; Villetti, Gino; Kendrick, Keith M.; Cuomo, Vincenzo
CORPORATE SOURCE: Department of Pharmacology and Human Physiology, University of Bari, Bari, Italy
SOURCE: J. Pharmacol. Exp. Ther. (2000), 294(1), 187-194
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1,2,3,3A,8,8a-Hexahydro-1,3a,8-trimethylpyrrolo[2,3-b]indol-5-ol 2-ethylphenylcarbamate N-oxide hydrochloride (3aS-cis) (CHF2819) is a novel acetylcholinesterase inhibitor that produces central cholinergic stimulation after oral administration in rats. In vivo studies show that CHF2819 (0.5, 1.5, and 4.5 mg/kg p.o.) significantly increases acetylcholine levels in young adult rat hippocampus in a dose-dependent manner. Moreover, aged animals, which show a significant decrease in basal acetylcholine levels with respect to young adult rats, also exhibit a marked increase in the hippocampal concns. of this neurotransmitter after the administration of CHF2819. This compd. (1.5 mg/kg p.o.) significantly attenuates scopolamine-induced amnesia in a passive avoidance task. Furthermore, CHF2819 induces a significant decrease in dopamine levels and a significant elevation of extracellular concns. of 5-hydroxytryptamine, whereas it does not modify norepinephrine and .gamma.-aminobutyric acid levels in the hippocampus of young adult rats. Functional observational battery screening demonstrates that CHF2819 (1.5 and 4.5 mg/kg p.o.) does not affect activity, excitability, autonomic, neuromuscular, and sensorimotor domains, as well as physiol. end points (body wt. and temp.). However, this compd. induces involuntary motor movements (ranging from mild tremors to myoclonic jerks) in a dose-dependent manner. These findings suggest that the anti-amnestic properties of CHF2819, together with its stimulatory effect on cholinergic and serotonergic functions, might have a therapeutic potential mainly for the symptomatic treatment of Alzheimer's disease patients in which the cognitive impairment is accompanied by a depressive syndrome.

IT **9000-81-1, Acetylcholinesterase**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; biochem. and neurobehavioral profile of CHF2819, orally active **acetylcholinesterase inhibitor** for

Alzheimer's disease)
REFERENCE COUNT: 47
REFERENCE(S): (2) Beani, L; J Pharmacol Exp Ther 1986, V236, P230 CAPLUS
(3) Bianchi, C; Naunyn-Schmiedeberg's Arch Pharmacol 1982, V318, P253 CAPLUS
(4) Cagiano, R; Br J Pharmacol 1998, V125, P909 CAPLUS
(5) Camacho, F; Psychopharmacology 1996, V124, P347 CAPLUS
(6) Chu, D; Neurosci Lett 1987, V82, P246 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 36 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:306973 CAPLUS
DOCUMENT NUMBER: 133:144735
TITLE: Protective effect of L-phenylalanine on rat brain **acetylcholinesterase inhibition** induced by free radicals
AUTHOR(S): Tsakiris, Stylianos; Angelogianni, Panagoula; Schulpis, Kleopatra H.; Stavridis, John C.
CORPORATE SOURCE: Department of Experimental Physiology, Medical School, University of Athens, Athens, GR-154 01, Greece
SOURCE: Clin. Biochem. (2000), 33(2), 103-106
CODEN: CLBIAS; ISSN: 0009-9120
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It was investigated whether the preincubation of brain homogenates with L-Phe (Phe) could reverse the free radical effects on brain acetylcholinesterase (AChE) activity, since it was reported that Phe binds hydroxyl radicals (.cntdot.OH). 2 Well established systems were used for prodn. of free radicals: (a) FeSO4 (84 .mu.M) plus ascorbic acid (400 .mu.M), and (b) FeSO4, ascorbic acid, and H2O2 (1 mM) at 37.degree.C in homogenates of adult rat whole brain. Changes in brain AChE activity were studied in the presence of each system sep. AChE was inhibited (18-28%) by both systems of free radicals. This inhibition was reversed when the brain homogenate was preincubated with Phe 1.8 mM. In accordance with the authors previous reports, Phe could protect against the direct action of .cntdot.OH radicals on brain AChE and in this way it might be useful in the prevention of certain cholinergic neural dysfunctions.
IT **9000-81-1, Acetylcholinesterase**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(protective effect of L-Phe on brain **acetylcholinesterase inhibition** induced by free radicals)
REFERENCE COUNT: 24
REFERENCE(S): (1) Adlard, B; J Neurochem 1973, V21, P877 CAPLUS
(2) Benzi, G; Neurochem Res 1989, V14, P473 CAPLUS
(3) Bowen, D; Br Med Bull 1986, V42, P75 CAPLUS
(6) Ghosh, C; Neurochem Int 1993, V23, P479 CAPLUS
(9) Harman, D; Age 1983, V6, P86 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 37 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:99765 CAPLUS
DOCUMENT NUMBER: 130:291473
TITLE: Improving effects of huperzine A on spatial working memory in aged monkeys and young adult monkeys with experimental cognitive impairment
AUTHOR(S): Ye, Jia Wei; Cai, Jing Xia; Wang, Li Ming; Tang, Xi Can
CORPORATE SOURCE: State Key Laboratory of Drug Research, Shanghai

Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, Peop. Rep. China
SOURCE: J. Pharmacol. Exp. Ther. (1999), 288(2), 814-819
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies demonstrated that huperzine A, a reversible and selective acetylcholinesterase inhibitor, exerts beneficial effects on memory deficits in various rodent models of amnesia. To further study the antiamnesic action of huperzine A in nonhuman primates, the drug was evaluated for its ability to reverse the deficits in spatial memory produced by scopolamine in young adult monkeys naturally occurring deficits in aged monkeys, using a delayed-response task. Scopolamine, a muscarinic receptor antagonist, dose dependently impaired performance, with the highest dose (0.03 mg/kg, i.m.) producing a significant redn. in choice accuracy in young adult monkeys. The delayed performance changed from an av. of 26.8/30 correct trials in controls to an av. of 20.2/30 after scopolamine administration. Huperzine A (0.01-0.1 mg/kg, i.m.) reversed the deficits induced by scopolamine in young adult monkeys on a delayed-response task; performance after an optimal dose (0.1 mg/kg) averaged 25.0/30 correct. In aged monkeys, huperzine A (0.001-0.01 mg/kg, i.m.) increased choice accuracy from 20.5/30 in controls to 25.2/30 at the optimal dose (0.001 mg/kg for 2 monkeys and 0.01 mg/kg for the other 2 monkeys). The beneficial effects of huperzine A on delayed-response performance were long lasting; performance remained improved for about 24 h after a single injection. This study extended to monkeys the findings that huperzine A improves mnemonic performance requiring working memory and suggests that huperzine A may be a promising agent for clin. therapy of cognitive impairments in patients with Alzheimer's disease.
IT **9000-81-1, Acetylcholinesterase**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; huperzine A improvement of spatial working memory in aged monkeys and adult monkeys with exptl. cognitive impairment)
REFERENCE COUNT: 42
REFERENCE(S):
(3) Bartus, R; Science (Wash DC) 1979, V206, P1087 CAPLUS
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(5) Bowen, D; J Neurochem 1983, V41, P266 CAPLUS
(6) Cheng, D; Neuroreport 1996, V8, P97 CAPLUS
(9) Decker, M; Synapse 1991, V7, P151 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 38 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:30238 CAPLUS
DOCUMENT NUMBER: 132:117461
TITLE: Nitrone spin trapping compound N-tert-butyl-.alpha.-phenylnitrone prevents seizures induced by anticholinesterases
AUTHOR(S): Zivin, Marko; Milatovic, Dejan; Dettbarn, Wolf-D.
CORPORATE SOURCE: Institute of Pathophysiology, Medical School, University of Ljubljana, Zaloska, 4, Slovenia
SOURCE: Brain Res. (1999), 850(1,2), 63-72
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
Searched by Barb O'Bryen, STIC 308-4291

AB The neuroprotection afforded by spin trapping agents such as N-tert-butyl-.alpha.-phenylnitrone (PBN) has lent support to the hypothesis that increased prodn. of reactive oxygen species (ROS) is a major contributing factor to excitotoxicity, aging and **cognitive** decline. Little is known, however, about the pharmacol. properties of PBN. We have compared the acute effects of PBN on the development of seizures induced by the irreversible acetylcholinesterase (AChE) inhibitor diisopropylphosphorofluoridate (DFP), the reversible AChE inhibitor physostigmine (PHY), the muscarinic cholinergic receptor agonist pilocarpine (PIL) and the glutamatergic receptor agonist kainic acid (KA). Rats were sacrificed 90 min after the injection of seizure-inducing agents. In situ hybridization was used to detect the induction of immediate early gene (IEG) c-fos and c-jun mRNA's and the levels of AChE mRNA. The activity of AChE was visualized by AChE staining and quantified using an in vitro AChE assay. The seizures correlated with the induction of IEG mRNA's with all agents used. The pre-treatment with 150 mg/kg of PBN prevented DFP- and PHY-induced seizures and the related expression of IEG mRNA's, but had no effect on PIL- or KA-induced seizures and assocd. IEG mRNA's changes. PBN prevented seizures and significantly protected AChE activity against DFP inhibition when given before, but not when given after DFP. This study shows that PBN specifically protects against anticholinesterase-induced seizures by reversible protection of AChE activity and not by the blockade of muscarinic or glutamate receptors, reactivation of AChE or scavenging of ROS. The anticholinesterase properties should be considered when using PBN in studies of cholinergic **dysfunction.**

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; nitrone spin trapping compd.
N-tert-butyl-.alpha.-phenylnitrone prevents seizures induced by anticholinesterases)

REFERENCE COUNT: 57
REFERENCE(S):
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(2) Andersen, K; J Appl Physiol 1996, V80, P862 CAPLUS
(3) Anderson, D; Biochem Biophys Res Commun 1993, V193, P878 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 39 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:807200 CAPLUS
DOCUMENT NUMBER: 132:146558
TITLE: Inhibitory effects of donepezil hydrochloride (E2020) on cholinesterase activity in brain and peripheral tissues of young and aged rats
AUTHOR(S): Kosasa, T.; Kuriya, Y.; Matsui, K.; Yamanishi, Y.
CORPORATE SOURCE: Tsukuba Research Laboratories, Eisai, Tsukuba, Ibaraki, Japan
SOURCE: Eur. J. Pharmacol. (1999), 386(1), 7-13
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Donepezil hydrochloride (donepezil: E2020: (.+-.)-2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-indan-1-one monohydrochloride) is a centrally acting acetylcholinesterase inhibitor developed for the treatment of Alzheimer's disease. In the present study, its inhibitory effect on the activity of cholinesterase ex vivo was evaluated in the brain, plasma, erythrocytes, heart, small intestine, liver and pectoral muscle of young adult as well as aged rats, in comparison with that of tacrine

(9-amino-1,2,3,4-tetrahydroacridine hydrochloride). In aged animals, cholinesterase activity in heart, small intestine and pectoral muscle was lower, whereas that in plasma and liver was higher than in young rats. Both groups showed the highest levels in the brain. Donepezil, at doses of 1.25, 2.5 and 5 mg/kg, p.o., inhibited brain, plasma, erythrocyte, liver and pectoral muscle cholinesterase activity in young rats in a dose-dependent manner but had less effect on cholinesterase activity in heart and small intestine. In aged animals, inhibition of cholinesterase activity in the brain, erythrocytes and pectoral muscle by donepezil was more potent than that in young animals. Tacrine, at doses of 5, 10 and 20 mg/kg, p.o., dose-dependently inhibited cholinesterase activity in all tissues of both young and aged animals, but most potently in heart, small intestine and liver. The inhibition of cholinesterase activity by tacrine in the brain, plasma, erythrocytes, heart and liver was more potent in aged rats than in tissues of young rats. Brain and plasma concns. of unchanged donepezil and tacrine were measured in the same animals as used for the cholinesterase inhibition study. Brain and plasma concns. of donepezil and tacrine were higher in aged than in young animals. It is concluded that the inhibitory effects of donepezil and tacrine on cholinesterase activity are greater in aged than in young rats, owing to differences in the tissue concns. of these compds. between young and aged animals. It is also suggested that the effect of donepezil on cholinesterase activity is more tissue-selective than that of tacrine.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(tissue-specific cholinesterase **inhibition** by donepezil in young and aged rats)

REFERENCE COUNT: 37
REFERENCE(S):
(1) Ambache, N; Biochem Pharmacol 1971, V20, P1123 CAPLUS
(2) Barner, E; Ann Pharmacother 1998, V32, P70 CAPLUS
(5) Brufani, M; Drugs of the Future 1997, V22, P397 CAPLUS
(8) Edwards, J; J Neurochem 1982, V38, P1393 CAPLUS
(9) Giacobini, E; Jpn J Pharmacol 1997, V74, P225 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 40 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:424362 CAPLUS
DOCUMENT NUMBER: 129:76516
TITLE: Pharmacogenetic methods for use in the treatment of nervous system diseases
INVENTOR(S): Poirier, Judes; Wiebusch, Heiko; Schappert, Keith
PATENT ASSIGNEE(S): McGill University, Can.; Nova Molecular, Inc.; Poirier, Judes; Wiebusch, Heiko; Schappert, Keith
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9827227	A2	19980625	WO 1997-IB1648	19971216
WO 9827227	A3	19980827		
W: AU, CA, JP, SG, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6022683	A	20000208	US 1996-766975	19961216
AU 9856757	A1	19980715	AU 1998-56757	19971216
EP 946753	A2	19991006	EP 1997-953011	19971216

Searched by Barb O'Bryen, STIC 308-4291

R: DE, FR, GB, SE
PRIORITY APPLN. INFO.: US 1996-766975 19961216
WO 1997-IB1648 19971216

AB The present invention provides a method for detg. the appropriate therapy and/or prognosis for a patient diagnosed with a neurol. disease. The present invention also provides a method for the identification of human subjects for placement in clin. drug trials of drugs being tested for the treatment of neurol. disease.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**inhibitors**; pharmacogenetic methods for use in treatment of nervous system diseases)

L164 ANSWER 41 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:349230 CAPLUS
DOCUMENT NUMBER: 129:90368
TITLE: Comparative studies of huperzine A, E2020, and tacrine on behavior and cholinesterase activities
AUTHOR(S): Cheng, Dong Hang; Tang, Xi Can
CORPORATE SOURCE: State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE: Pharmacol., Biochem. Behav. (1998), 60(2), 377-386
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Comparative effects of cholinesterase inhibitors (ChEI) huperzine A with E2020 and tacrine on the radial maze performance in ethylcholine mustard aziridinium ion (AF64A)-treated rat and inhibition of cholinesterase activity were studied. The intracerebroventricular (ICV) injection of AF64A (3 nmol/side) caused significant impairment in the rat's ability to fulfill the partially baited maze paradigm. Oral huperzine A (0.5-0.8 mg/kg), E2020 (1.0-2.0 mg/kg), and tacrine (8.0 mg/kg) effectively reversed AF64A-induced working memory deficit. The doses that improved AF64A-induced memory deficit were correlated to about 25-30% (huperzine A) and less than 10% (E2020, tacrine) inhibition of acetylcholinesterase (AChE) activity in the cortex and hippocampus. Huperzine A, E2020 and tacrine all produced dose-dependent inhibition of brain AChE following ICV and oral administration. Oral huperzine A exhibited higher efficacy on the inhibition of AChE in the cortex and hippocampus than those of E2020 and tacrine. Tacrine was more effective in inhibiting plasma butyrylcholinesterase (BuChE) than it was brain AChE. Conversely, the BuChE activity was less affected by huperzine A and E2020. The results showed that huperzine A had high bioavailability and more selective inhibition on AChE activity in cortex and hippocampus. Huperzine A fits more closely with the established criteria for an ideal AChE inhibitor to be used in clin. studies.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**inhibition**; comparative studies of huperzine A, E2020, and tacrine on behavior and cholinesterase activities)

L164 ANSWER 42 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:649517 CAPLUS
DOCUMENT NUMBER: 130:60934
TITLE: The effects of the acetylcholinesterase inhibitor, ENA713, and the M1 agonist AF150(S) on apolipoprotein E deficient mice
AUTHOR(S): Chapman, Shira; Fisher, Abraham; Weinstock, Marta; Brandies, Rachel; Shohami, Esther; Michaelson, Daniel M.
Searched by Barb O'Bryen, STIC 308-4291

CORPORATE SOURCE: Department of Neurobiochemistry, Tel-Aviv University, Tel-Aviv, Israel
SOURCE: J. Physiol. (Paris) (1998), 92(3-4), 299-303
CODEN: JHYSEM; ISSN: 0928-4257
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Apolipoprotein E (apoE)-deficient and control mice were treated chronically with either the acetylcholinesterase (AChE) inhibitor ENA713, or the M1 muscarinic agonist AF150(S). Both treatments reversed the spatial working memory impairment of apoE-deficient mice but they differed in their effects on the levels of brain AChE activity. AF150(S) enhanced the brain AChE activity of apoE-deficient mice and rendered it similar to that of the untreated controls, whereas ENA713 reduced the brain AChE activity of control mice but had no effect on that of apoE-deficient mice. These findings suggest that AChE inhibition and M1 muscarinic activation have similar beneficial cognitive effects on apoE-deficient mice, but that the cellular and mol. mechanisms underlying these effects differ.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**acetylcholinesterase inhibitor** ENA713 and M1 agonist AF150(S) effects on apolipoprotein E deficient mice)

REFERENCE COUNT: 16
REFERENCE(S):
(1) Chapman, S; J Neurochem 1998, V70, P708 CAPLUS
(2) Enz, A; Pharmacological interventions on central cholinergic mechanisms in senile dementia 1989, P271 CAPLUS
(3) Fisher, A; Exp Opin Invest Drugs 1997, V6, P1395 CAPLUS
(6) Giacobini, E; Progr Brain Res 1996, V109, P311 CAPLUS
(7) Gordon, I; Neurosci Lett 1995, V199, P1 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L164 ANSWER 43 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:108744 CAPLUS
DOCUMENT NUMBER: 128:200972
TITLE: Phenserine, a novel **acetylcholinesterase inhibitor**, attenuates impaired learning of rats in a 14-unit T-maze induced by blockade of the N-methyl-D-aspartate receptor
AUTHOR(S): Patel, Namisha; Spangler, Edward L.; Greig, Nidel H.; Yu, Quan-Sheng; Ingram, Donald K.; Meyer, Robert C.
CORPORATE SOURCE: Molecular Physiology and Genetics Section, Johns Hopkins University, Baltimore, MD, USA
SOURCE: NeuroReport (1998), 9(1), 171-176
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study evaluated the interaction of the glutamatergic and acetylcholinergic systems in memory formation, with an overall emphasis on developing multi-system approaches for treating age-related cognitive decline and Alzheimer's disease. Specifically, we used a 14-unit T-maze to investigate whether phenserine (PHEN), a long-acting acetylcholinesterase inhibitor, could overcome a learning deficit in rats induced by the NMDA receptor antagonist, 3-(.+-.)-2-carboxypiperzin-4-yl-propylphosphonic acid (CPP). Prior to drug treatment, 3-mo-old male Fischer-344 rats were trained to criterion (13 of 15 shock avoidances) in a straight runway. Twenty-four hours later, rats were given i.p. injections of saline (SAL), CPP (9 mg/kg) + SAL or CPP + PHEN (0.25, 0.5 or 0.75 mg/kg) and received 15 massed

training trials in a 14-unit T-maze. CPP significantly increased the no. of errors made in the maze relative to controls, and phenserine significantly reduced the no. of errors made relative to rats receiving CPP only, with the lowest dose being the most effective. These results provide further support of phenserine's potent, cognitive-enhancing properties, and suggest that combined modulation of glutamatergic and acetylcholinergic systems may be of potential benefit in developing new pharmacotherapies for Alzheimer's disease and **age-related** cognitive decline.

L164 ANSWER 44 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:380597 CAPLUS
DOCUMENT NUMBER: 129:117703
TITLE: Reversal of scopolamine-induced deficits in radial maze performance by (-)-huperzine A: comparison with E2020 and tacrine
AUTHOR(S): Wang, Tie; Tang, Xi Can
CORPORATE SOURCE: Shanghai Institute of Materia Medica, State Key Laboratory of Drug Research, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE: Eur. J. Pharmacol. (1998), 349(2/3), 137-142
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of (-)-huperzine A, E 2020, and tacrine on scopolamine-induced memory deficits in rats were compared in a radial maze, using a 4-out-of-8 baiting procedure. Scopolamine (0.15 mg/kg, i.p.) impaired the rats' ability to fulfil the radial maze task. (-)-Huperzine A (0.2-0.4 mg/kg, orally; 0.1-0.4 mg/kg, i.p.) had greater efficacy than E2020 (0.6-0.9 mg/kg, orally; 0.3-0.6 mg/kg, i.p.) and tacrine (1.5-2.5 mg/kg, orally; 0.3-0.6 mg/kg, i.p.) on the improvement of scopolamine-induced working and ref. memory errors, resp. There appeared to be an inverse bell-shaped dose-dependent effect for all 3 compds. tested. The data demonstrate that (-)-huperzine A is the most potent and orally active acetylcholinesterase inhibitor of the 3 compds., and fits more closely the established criteria for an ideal acetylcholinesterase inhibitor to be used in clin. studies.
IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; scopolamine-induced memory deficits reversal by huperzine A as)

L164 ANSWER 45 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:196193 CAPLUS
DOCUMENT NUMBER: 129:461
TITLE: Effect of the subchronic treatment with the **acetylcholinesterase inhibitor** heptastigmine on central cholinergic transmission and memory impairment in aged rats
AUTHOR(S): Garrone, B.; Luparini, M. R.; Tolu, L.; Magnani, M.; Landolfi, C.; Milanese, C.
CORPORATE SOURCE: Laboratory of Neuropharmacology, Angelini Research, Rome, Italy
SOURCE: Neurosci. Lett. (1998), 245(1), 53-57
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of subchronic administration of the acetylcholinesterase (AChE) inhibitor heptastigmine (HEP 0.6 mg/kg s.c. daily for 15 days) was investigated on cortical extracellular acetylcholine (ACh) levels and on memory function in aged male rats (26 mo old at the beginning of the

expts.) using microdialysis and behavioral techniques. Twenty-four hours after the last treatment, cortical ACh levels were significantly higher in rats subchronically treated with HEP than in rats treated with saline and AChE activity was still inhibited in cortex, hippocampus and striatum. The injection of a challenge dose of HEP (0.6 mg/kg s.c.) 24 h after the last treatment produced a faster and a more sustained increase of ACh in the cortex of subchronically treated rats compared to those repeatedly injected with saline. However, the max. increase of ACh levels after injection of the challenge was comparable in both groups. In an object recognition test in which the pretest and test phase were spaced by 45 days, HEP prevented the deterioration of spatial memory occurring during this period, but had no effect on non-spatial memory. The present results suggest that moderate inhibition of brain AChE is able to maintain high levels of cortical extracellular ACh in aged rats and that this increase matches facilitatory effect of HEP on spatial memory.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effect of subchronic treatment with the **acetylcholinesterase inhibitor** heptastigmine on central cholinergic transmission and memory impairment in aged rats)

L164 ANSWER 46 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:533469 CAPLUS
DOCUMENT NUMBER: 129:254877
TITLE: Effect of subchronic treatment with metrifonate and tacrine on brain cholinergic function in aged F344 rats
AUTHOR(S): Giovannini, Maria Grazia; Scali, Carla; Bartolini, Luciano; Schmidt, Bernard; Pepeu, Giancarlo
CORPORATE SOURCE: Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, 50134, Italy
SOURCE: Eur. J. Pharmacol. (1998), 354(1), 17-24
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of 21-day treatment with the acetylcholinesterase inhibitors metrifonate (80 mg kg-1 per os (p.o.)) and tacrine (3 mg kg-1 p.o.), twice daily, on cortical and hippocampal cholinergic systems were investigated in aged rats (24-26 mo). Extracellular acetylcholine levels were measured by transversal microdialysis in vivo; choline acetyltransferase and acetylcholinesterase activities were measured ex vivo by radiometric methods. Basal cortical and hippocampal extracellular acetylcholine levels, measured 18 h after the last metrifonate treatment, were about 15 and two folds higher, resp., than in control and tacrine-treated rats. A challenge with metrifonate further increased cortical and hippocampal acetylcholine levels by about three and four times, resp. Basal extracellular acetylcholine levels, measured 18 h after the last treatment with tacrine were not statistically different from those of the control rats. A challenge with tacrine increased cortical and hippocampal extracellular acetylcholine levels by about four and two times. A 75% inhibition of cholinesterase activity was found 18 h after the last metrifonate administration, while only a 15% inhibition was detectable 18 h after the last tacrine administration. The challenge with metrifonate or tacrine resulted in 90 and 80% cholinesterase inhibition, resp. These results demonstrate that in aging rats a subchronic treatment with metrifonate results in a long-lasting, cholinesterase inhibition, and a persistent increase in acetylcholine extracellular levels which compensate for the age-assocd. cholinergic hypofunction. Metrifonate is therefore a potentially useful agent for the cholinergic deficit accompanying Alzheimer's disease.

IT **9000-81-1, Acetylcholinesterase**

Searched by Barb O'Bryen, STIC 308-4291

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(subchronic treatment with metrifonate enhances brain cholinergic function in aged F344 rats in relation to **inhibition** of)

L164 ANSWER 47 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:539121 CAPLUS
DOCUMENT NUMBER: 129:285896
TITLE: The clinical trial protocol of the Metrifonate in ALzheimer's Trial (MALT)
AUTHOR(S): McKeith, Ian G.
CORPORATE SOURCE: Newcastle General Hospital, Newcastle-upon-Tyne, UK
SOURCE: Dementia Geriatr. Cognit. Disord. (1998), 9(Suppl. 2, Current Perspectives in the Diagnosis and Treatment of Alzheimer's Disease), 2-7
CODEN: DGCDFX; ISSN: 1420-8008
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The promising results of early trials in Alzheimer's disease with the acetylcholinesterase inhibitor metrifonate prompted initiation of the Metrifonate in ALzheimer's Trial (MALT). MALT is an international, randomized, double-blind, placebo-controlled, parallel-group study which was designed to det., over a 26-wk period, the efficacy, tolerability and safety of 2 doses of metrifonate in patients with probable Alzheimer's disease. A total of 605 patients were randomized to receive either a daily oral dose of metrifonate at 40/50 mg (by body wt. <65 kg/.gtoreq.65 kg) or metrifonate at 60/80 mg (by body wt. <65 kg/.gtoreq.65 kg). The patients were assessed in the key symptom domains of Alzheimer's disease, i.e., cognition, behavioral and psychiatric disturbances, activities of daily living and global function. Administration of metrifonate for 26 wk benefited cognitive performance, global function and certain aspects of behavior and functional ability compared with placebo. These efficacy results were assocd. with high levels of acetylcholinesterase inhibition and a good safety and tolerability profile. The protocol of MALT is discussed.
IT **9000-81-1, Acetylcholinesterase**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; Alzheimers's disease of humans treatment by metrifonate as)

L164 ANSWER 48 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:617007 CAPLUS
DOCUMENT NUMBER: 127:288186
TITLE: Methods of treating neurological diseases and etiologically related symptomology using carbonyl trapping agents in combination with previously known medicaments
INVENTOR(S): Shapiro, Howard K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 37 pp. Cont.-in-part of U.S. Ser. No. 26,617, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5668117	A	19970916	US 1993-62201	19930629

Searched by Barb O'Bryen, STIC 308-4291

WO 9501096	A1	19950112	WO 1994-US7277	19940628
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2166383	AA	19950112	CA 1994-2166383	19940628
AU 9472144	A1	19950124	AU 1994-72144	19940628
AU 692454	B2	19980611		
EP 707446	A1	19960424	EP 1994-921405	19940628
R: DE, FR, GB, IT				
JP 08512055	T2	19961217	JP 1994-503597	19940628
PRIORITY APPLN. INFO.:			US 1991-660561	19910222
			US 1993-26617	19930223
			US 1993-62201	19930629
			WO 1994-US7277	19940628

OTHER SOURCE(S): MARPAT 127:288186

AB Therapeutic compns. comprising an effective amt. of at least one carbonyl trapping agent alone or in combination with a therapeutically effective of a co-agent or medicament are disclosed. The compns. are used to treat a mammal suffering from a neurol. disease characterized by covalent bond crosslinking between the nerve cells, other cellular structures and their intracellular and extracellular components, with disease-induced carbonyl-contg. aliph. or arom. hydrocarbons present in mammals.

IT **9000-81-1, Acetylcholinesterase**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; carbonyl trapping agent combination with other drug for treatment of neurol. diseases and etiol. related symptomol.)

L164 ANSWER 49 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:21377 CAPLUS
DOCUMENT NUMBER: 128:97719
TITLE: Use of darifenacin to enhance cognitive functions
INVENTOR(S): Allen, Michael John; Johnson, Brian Frank; Leaker, Brian Robert; Wallis, Robert Michael
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 813870	A1	19971229	EP 1997-303879	19970605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 10059848	A2	19980303	JP 1997-151899	19970610
US 5837724	A	19981117	US 1997-872891	19970611
CA 2208111	AA	19971218	CA 1997-2208111	19970616
AU 9724956	A1	19980108	AU 1997-24956	19970617
ZA 9705311	A	19981217	ZA 1997-5311	19970617
PRIORITY APPLN. INFO.:			GB 1996-12710	19960618

AB Darifenacin, and its pharmaceutically acceptable salts, are useful in the treatment of cognitive impairment. The invention also discloses the use of combinations of darifenacin, or a pharmaceutically acceptable salt thereof, with an acetylcholinesterase inhibitor (e.g. donepezil), in the treatment of cognitive impairment.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; darifenacin combination with **acetylcholinesterase inhibitor** to enhance cognitive functions)

Searched by Barb O'Bryen, STIC 308-4291

L164 ANSWER 50 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:735087 CAPLUS
DOCUMENT NUMBER: 128:43758
TITLE: Metrifonate improves associative learning and retention in aging rabbits
AUTHOR(S): Kronforst-Collins, M. A.; Moriearty, P. L.; Schmidt, B.; Disterhoft, J. F.
CORPORATE SOURCE: Department of Cell and Molecular Biology, Institute for Neuroscience, Northwestern University Medical School, Chicago, IL, 60611-3008, USA
SOURCE: Behav. Neurosci. (1997), 111(5), 1031-1040
CODEN: BENEDJ; ISSN: 0735-7044
PUBLISHER: American Psychological Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cholinergic system is known to show deterioration during aging and Alzheimer's disease (AD). In response, a therapeutic approach to AD has been to attempt to compensate for the decrease in central cholinergic function by potentiating the activity of the remaining intact cholinergic cells with cholinesterase (ChE) inhibitors. In this study treatment with the long-lasting ChE inhibitor metrifonate facilitated acquisition and retention of eyeblink conditioning in aging rabbits. Metrifonate treatment resulted in steady-state, dose-dependent acetylcholinesterase (AChE) inhibition in red blood cells. Maximal behavioral efficacy was achieved with AChE inhibition of approx. 40%, with no further improvements resulting from increased levels of inhibition. Metrifonate was behaviorally effective in the absence of the severe side effects that can plague ChE inhibitors, supporting metrifonate as a possible treatment for the cognitive deficits resulting from normal aging and AD.
IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metrifonate improves associative learning and retention in aging rabbits in relation to **acetylcholinesterase inhibition** and treatment of Alzheimer's disease)

L164 ANSWER 51 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:242145 CAPLUS
DOCUMENT NUMBER: 126:271701
TITLE: Donepezil
AUTHOR(S): Bryson, Harriet M.; Benfield, Paul
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs Aging (1997), 10(3), 234-239
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 26 refs. Donepezil is a specific and potent acetylcholinesterase inhibitor according to in vitro data. It displays primarily noncompetitive inhibitory activity. In vivo, donepezil inhibited acetylcholinesterase activity in human erythrocytes and increased extra-cellular acetylcholine levels in the cerebral cortex and hippocampus of the rat. Donepezil demonstrated efficacy in tests of ref. memory in animals, but had less consistent activity in tests of working memory. Donepezil 5 or 10 mg/day was assocd. with significant improvements in cognitive function [assessed by the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog)] after 14 and 30 wk and patient global function (Clinician's Interview-based Impression of Change incorporating caregiver input score) after 30 wk, compared with placebo, in patients with mild to moderate Alzheimer's disease. After 2 yr, donepezil 5 or 10 mg/day was assocd. with an ADAS-cog score approx. 4 points better than would be expected in untreated patients with mild to

moderate Alzheimer's disease. The most common adverse events reported in assocn. with donepezil 5 mg/day were gastrointestinal events (nausea/vomiting, diarrhea, gastric upset and constipation) and dizziness. No hepatotoxicity was reported after 12 wk' treatment.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; donepezil pharmacodynamics and pharmacokinetics)

L164 ANSWER 52 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:123307 CAPLUS
DOCUMENT NUMBER: 126:220296
TITLE: Synthesis and preliminary structure-activity relationships of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-1H-indol-5-yl methyl carbamate (P10358), a novel **acetylcholinesterase inhibitor**
AUTHOR(S): Martin, Lawrence L.; Davis, Larry; Klein, Joseph T.; Nemoto, Peter; Olsen, Gordon E.; Bores, Gina M.; Camacho, Fernando; Petko, Wayne W.; Rush, Douglas K.; et al.
CORPORATE SOURCE: Hoechst Marion Roussel Inc., Neuroscience Therapeutic Area, Bridgewater, NJ, 08807-0800, USA
SOURCE: Bioorg. Med. Chem. Lett. (1997), 7(2), 157-162
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of carbamate analogs of besipirdine (HP 749) was synthesized as potential agents with enhanced cholinomimetic properties for the treatment of Alzheimer's disease. P10358, 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-1H-indol-5-yl Me carbamate, emerged as a potent, reversible acetylcholinesterase inhibitor that significantly enhanced performance on oral or parenteral administration in learning and memory paradigms.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and structure-activity relationships of besipirdine carbamate analogs as **acetylcholinesterase inhibitors**
)

L164 ANSWER 53 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:32874 CAPLUS
DOCUMENT NUMBER: 126:70052
TITLE: Effect of TAK-147, a novel AChE inhibitor, on cerebral energy metabolism
AUTHOR(S): Nakayama, Takahiro; Takahashi, Hideki; Miyamoto, Masaomi; Goto, Giichi; Nagai, Yasuo
CORPORATE SOURCE: Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
SOURCE: Neurobiol. Aging (1996), 17(6), 849-857
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effect of TAK-147, a novel acetylcholinesterase (AChE) inhibitor, on cerebral energy metab. was investigated using an in vivo 31P-magnetic resonance spectroscopy (31P-MRS) technique and the autoradiog. 2-deoxy-[14C]-D-glucose method in aged Fischer 344 rats. We revealed that high-energy phosphate metabolites, phosphocreatine (PCr) and ATP, in the brain decreased gradually with aging and that significant decrement of cerebral PCr and ATP was obsd. from 13- and 8.5-mo-old in comparison with those of 2.5-mo-old rats, resp. Daily oral administration of TAK-147 (1 mg/kg) for 40 days increased PCr and ATP levels in aged rats (29-mo-old). To det. the site at which TAK-147 acts to increase high-energy phosphate

metab., we investigated the rate of local cerebral glucose utilization (LCGU) in various brain regions. The rate of LCGU decreased in almost all brain regions in aged rats (28 mo of age), and the decrease was significant in 29 out of the 35 regions. When TAK-147 was administered orally to the aged rats, the levels were dose dependently increased, esp. in the auditory cortex. These results indicate that TAK-147 increases cerebral energy metab. in aged rats.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; effect of **acetylcholinesterase inhibitor** TAK-147 on cerebral energy metab. in aged rats)

L164 ANSWER 54 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:193684 CAPLUS
DOCUMENT NUMBER: 126:207463
TITLE: Huperzine A, a novel promising **acetylcholinesterase inhibitor**
AUTHOR(S): Cheng, Dong Hang; Ren, Hua; Tang, Xi Can
CORPORATE SOURCE: State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE: NeuroReport (1996), 8(1), 97-101
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of huperzine A (I) on memory impairments (amnesia) induced by scopolamine (a model for human dementia) were evaluated using a radial maze task and inhibition of cholinesterase in vitro compared with the effects of E 2020 (II) and tacrine (III). Scopolamine (0.2 mg/kg) significantly impaired spatial memory in rats. I (0.1-0.4 mg/kg, p.o.), II (0.5-1.0 mg/kg, p.o.) and IIIe (1.0-2.0 mg/kg, p.o) were able to reverse these scopolamine-induced memory deficits. The ratios of I, II, and III for butyrylcholinesterase:acetylcholinesterase detd. by a colorimetric method were 884.57, 489.05, and 0.80, resp. The results demonstrated that I was the most selective acetylcholinterase inhibitor, and improved the working memory deficit induced by scopolamine significantly better than did II or III, suggesting it may be a promising agent for clin. therapy of cognitive impairment in patients with Alzheimer's disease.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(huperzine A, a novel promising **acetylcholinesterase inhibitor** for clin. therapy of cognitive impairment in patients with Alzheimer's disease)

L164 ANSWER 55 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000037532 EMBASE
TITLE: Regulating and assessing risks of cholinesterase-inhibiting pesticides: Divergent approaches and interpretations.
AUTHOR: Carlock L.L.; Chen W.L.; Gordon E.B.; Killeen J.C.; Manley A.; Meyer L.S.; Mullin L.S.; Pendino K.J.; Percy A.; Sargent D.E.; Seaman L.R.; Svanborg N.K.; Stanton R.H.; Tellone C.I.; Van Goethem D.L.
CORPORATE SOURCE: L.L. Carlock, Toxicology and Regulatory Consulting, 6343 38th Ave. S.W., Seattle, WA 98126, United States
SOURCE: Journal of Toxicology and Environmental Health - Part B, (1999) 2/2 (105-160).
Refs: 69
ISSN: 1093-7404 CODEN: JTECFR
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review

Searched by Barb O'Bryen, STIC 308-4291

FILE SEGMENT: 052 Toxicology
037 Drug Literature Index
035 Occupational Health and Industrial Medicine
029 Clinical Biochemistry
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This document presents a revised framework for conducting worker and dietary risk assessments for less-than-lifetime exposures to organophosphate or carbamate pesticides based on red blood cell (RBC) or brain **acetylcholinesterase** (AChE) inhibition or the presence of clinical signs and symptoms. The proposals for appropriate uncertainty factors are based on the biological significance of the cholinesterase (ChE) inhibition noted at the lowest-observed-effect level (LOEL) and the degree of uncertainty in the extrapolation between human and animal data. An extensive evaluation of industry data, not previously summarized, and the available literature indicate that the following risk assessment principles are supportable and protective of human health: Plasma ChE inhibition is not an adverse effect, and therefore should not be utilized in risk assessments. Red blood cell AChE is not associated with the nervous system and inhibition is not per se an adverse (neurotoxic) effect. When available, cholinergic effects or brain AChE inhibition data should take precedence over RBC AChE for determining no-observed-effect levels (NOELs). When available, human RBC AChE inhibition or cholinergic effects data should take precedence over animal data for determining NOELs. Due to the lack of adversity associated with inhibition of RBC AChE, the use of a 10-fold (10x) uncertainty factor from the NOEL is adequate when RBC AChE inhibition data from either animal or human studies are used to assess human risk. Due to greater potential for adversity, NOELs for brain AChE inhibition and cholinergic effects identified in animal studies should receive a default uncertainty factor of 100x; lower uncertainty factors may be used on a case-by-case basis. NOELs based on cholinergic effects noted in human studies should only require a 10x uncertainty factor, since an interspecies extrapolation factor from animals to humans is unnecessary. For RBC and brain AChE activity the threshold for defining a NOEL should be less than or equal to 20% difference from control activity in all species. For risk assessment purposes, duration and route of the study should reflect the expected duration and route of exposure for humans (i.e., a 21-d or 28-d dermal study for subchronic occupational dermal exposure assessment). When dermal data are not available, a subchronic oral toxicity study and an appropriate dermal penetration factor should be used. A general default of 10% absorption should be used, analogous to the United Kingdom and German exposure models that are widely used in Europe. The recommendations in this document are generally consistent with current risk assessment procedures used by Canada, the European Community (EC), and the United Kingdom (UK).

L164 ANSWER 56 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999327523 EMBASE
TITLE: The **acetylcholinesterase** inhibitor, ENA 713 (Exelon), attenuates the working memory impairment induced by scopolamine in an operant DNMTP task in rats.
AUTHOR: Ballard T.M.; McAllister K.H.
CORPORATE SOURCE: K.H. McAllister, Novartis Pharma Inc., Nervous System Department, WSJ-386.226, CH-4002 Basel, Switzerland. Kevin.McAllister@pharma.novartis.com
SOURCE: Psychopharmacology, (1999) 146/1 (10-18).
Refs: 36
ISSN: 0033-3158 CODEN: PSCHDL
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
Searched by Barb O'Bryen, STIC 308-4291

FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Rationale: The disruption of working memory in the delayed non-matching to position (DNMTP) task by the muscarinic antagonist, scopolamine, is considered to be a model of the spatial working memory deficit in Alzheimer's disease (AD) patients. Objective: To investigate whether ENA 713 (Exelon) (0.1, 0.5 mg/kg, IP), an **acetylcholinesterase** inhibitor, would reverse the effects of scopolamine in the DNMTP task. Methods: Male Lister Hooded rats were trained to criterion in an operant DNMTP task (0- to 16-s delay intervals) before receiving vehicle, scopolamine (0.05 mg/kg, SC) alone, ENA 713 (0.1, 0.5 mg/kg, IP) alone, or combinations of scopolamine and ENA 713, in two variations of the task - with and without barriers inserted between the food magazine and the two levers. Barriers were inserted to prevent the use of positional strategies to perform the task, since this behaviour may confound the conclusions of the effect of drugs on working memory. Results: It was found that: (i) scopolamine significantly reduced choice accuracy delay-dependently in both test situations while modifying non-mnemonic measures of task performance delay-independently, indicating an impairment of working memory; (ii) ENA 713 (0.5 mg/kg) significantly attenuated the scopolamine-induced impairment of working memory and significantly reduced the scopolamine-induced changes in some non-mnemonic measures of task performance; (iii) the presence of barriers did not alter the effects of scopolamine and ENA 713 on working memory. Conclusion: ENA 713 reversed the working memory deficit induced by scopolamine. These results are consistent with the attenuation of learning and memory disruptions due to cholinergic dysfunction by ENA 713 in other preclinical assays, and predict a drug- induced improvement in working memory in AD patients.

L164 ANSWER 57 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998265002 EMBASE
TITLE: Shuttle-box avoidance learning in mice: Improvement by combined glucose and tacrine.
AUTHOR: Pavone F.; Capone F.; Battaglia M.; Sansone M.
CORPORATE SOURCE: F. Pavone, Ist. Psicobiologia Psicofarmacol., CNR, Via Reno 1, 00198 Roma, Italy. pavone@vaxiac.iac.rm.cnr.it
SOURCE: Neurobiology of Learning and Memory, (1998) 69/2 (204-210). Refs: 20
ISSN: 1074-7427 CODEN: NLMEFR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Glucose and the **acetylcholinesterase** inhibitor tacrine were tested, alone and in combination, in mice of the CD-1 strain subjected to five daily shuttle-box training sessions. Pretraining intraperitoneal administration of glucose alone (50-400 mg/kg) had no significant effect, while tacrine alone (0.5-3 mg/kg) improved avoidance acquisition at the dose of 2 mg/kg only. Significant avoidance learning improvements were instead produced by 50 or 100 mg/kg glucose combined with 0.5 or 1 mg/kg tacrine. The effects on shuttle-box avoidance acquisition produced by glucose combined with a cholinomimetic agent support the hypothesis that cholinergic mechanisms may be involved in the action of glucose on learning and memory. However, the main finding of the present study is related to the enhancement by glucose of the learning improving action of a drug clinically used as cognitive enhancer.

L164 ANSWER 58 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999011077 EMBASE
TITLE: Learning and memory of rats after long-term administration of low doses of parathion.
AUTHOR: Ivens I.A.; Schmuck G.; Machemer L.
CORPORATE SOURCE: I.A. Ivens, Preclinical Research, Bayer Corporation, Berkeley, CA 94710, United States
SOURCE: Toxicological Sciences, (1998) 46/1 (101-111).
Refs: 71
ISSN: 1096-6080 CODEN: TOSCF2
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A set of four learning and memory tests (Morris Maze I for reference memory, Morris Maze II for working memory, one-way active avoidance, and passive avoidance) were employed to address the questions whether parathion impaired cognitive functions after low, long-term exposure and could cause persistent changes in cognition. Motor activity and general behavior were investigated in a functional observational battery. Parathion was administered in rat food in low doses which caused no clinical symptoms and no or borderline brain **acetylcholinesterase** inhibition. Parathion doses of 0.5, 2, or 8 ppm in rat food produced the averaged uptake of 24, 100, or 400 .mu.g/kg body weight per group per day in male rats and 36, 152, or 550 .mu.g/kg per day in female rats in week 13. Learning tests were performed in weeks 1 to 4 and 10 to 14, as well as 30 to 34 weeks after the end of treatment, when the male and female rats were about 13 months old. Low doses of parathion given daily for 13 weeks had no cumulative or adverse effects on learning and memory, either during treatment or after the extended treatment-free period, in any of the tests. A significant improvement of learning compared to control observed in the Morris Water Maze I during the first week of treatment (males dose group 0.5 ppm) shows that parathion can improved cognitive functions in rats. Results of the study indicate that adverse effects changing learning and memory in animals may occur only at higher doses of organophosphates, at which the peripheral and brain **acetylcholinesterases** are inhibited to a greater extent than those in the present study.

L164 ANSWER 59 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97192085 EMBASE
DOCUMENT NUMBER: 1997192085
TITLE: Cholinergic stimulation alters performance and task-specific regional cerebral blood flow during working memory.
AUTHOR: Furey M.L.; Pietrini P.; Haxby J.V.; Alexander G.E.; Lee H.C.; VanMeter J.; Grady C.L.; Shetty U.; Rapoport S.I.; Schapiro M.B.; Freo U.
CORPORATE SOURCE: M.L. Furey, Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, United States.
kurkjian@alw.nih.gov
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/12 (6512-6516).
Refs: 36
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
LANGUAGE: English
Searched by Barb O'Bryen, STIC 308-4291

SUMMARY LANGUAGE: English
AB Modulation of the cholinergic neurotransmitter system results in changes in memory performance, including working memory (WM), in animals and in patients with Alzheimer disease. To identify associated changes in the functional brain response, we studied performance measures and regional cerebral blood flow (rCBF) using positron emission tomography (**PET**) in healthy subjects during performance of a WM task. Eight control subjects received an infusion of saline throughout the study and 13 experimental subjects received a saline infusion for the first 2 scans followed by a continuous infusion of physostigmine, an **acetylcholinesterase** inhibitor, for the subsequent 8 scans. rCBF was measured using H215O and **PET** in a sequence of 10 **PET** scans that alternated between rest and task scans. During task scans, subjects performed the WM task for faces. Physostigmine both improved WM efficiency, as indicated by faster reaction times, and reduced WM task-related activity in anterior and posterior regions of right midfrontal gyrus, a region shown previously to be associated with WM. Furthermore, the magnitudes of physostigmine-induced change in reaction time and right midfrontal rCBF correlated. These results suggest that enhancement of cholinergic function can improve processing efficiency and thus reduce the effort required to perform a WM task, and that activation of right prefrontal cortex is associated with task effort.

L164 ANSWER 60 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97116902 EMBASE
DOCUMENT NUMBER: 1997116902
TITLE: Effects of 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1H- 1-benzazepin-8-yl)-1-propanone fumarate (TAK-147), a novel **acetylcholinesterase** inhibitor, on impaired learning and memory in animal models.
AUTHOR: Miyamoto M.; Takahashi H.; Kato K.; Hirai K.; Ishihara Y.; Goto G.
CORPORATE SOURCE: Dr. M. Miyamoto, Pharmaceutical Research Lab. I, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2-17-85 Juso-honmachi, Yodogawa-ku, Osaka 532, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1996) 277/3 (1292-1304).
Refs: 78
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We examined the effects of p.o. administered 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone fumarate (TAK-147), a novel AChE inhibitor, on impaired learning and memory in animal models. At 1 to 3 mg/kg, TAK-147 ameliorated the passive avoidance deficit induced by diazepam. TAK-147 did not affect delayed-matching-to-position (DMTP) performance of normal rats at doses of 1 to 30 mg/kg assessed by using a three-lever operant chamber, but 9-amino-tetrahydroacridine disrupted the DMTP response at 5 to 20 mg/kg. Scopolamine (0.02-0.1 mg/kg s.c.) impaired DMTP performance, whereas methylscopolamine did not affect the DMTP task. TAK-147 ameliorated the impairment of DMTP performance induced by scopolamine without affecting the general behavior of the rats; however, 9-amino- tetrahydroacridine produced no significant amelioration of the impairment. The intraventricular injection of AF64A disrupted differential-reinforcement-

of-low-rate 10-sec performance in rats, as demonstrated by marked decreases in reinforcement rate and response efficiency. TAK-147 slightly increased the reinforcement rate in AF64A-treated rats at a low dose of 1 mg/kg, but the effect was not significant statistically. TAK-147 had no significant effect on the duration of immobility in rats in a forced swimming test at doses of 2 to 10 mg/kg. 9-Aminotetrahydroacridine prolonged the duration of immobility at 5 to 20 mg/kg. Furthermore, TAK-147 reversed reserpine-induced hypothermia and ptosis in mice at doses of 3 to 10 mg/kg, a result that implies an antidepressant-like action. These results indicate that TAK-147 ameliorates learning and memory impairment in animal models without affecting the general behavior or causing behavioral depression and suggest that TAK-147 may be useful for the treatment of Alzheimer's disease.

L164 ANSWER 61 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94256749 EMBASE
DOCUMENT NUMBER: 1994256749
TITLE: Cognition enhancer, **acetylcholinesterase** inhibitor.
AUTHOR: Prous J.; Rabasseda X.; Castaner J.
CORPORATE SOURCE: Prous Science Publishers, P.O. Box 540,08080 Barcelona, Spain
SOURCE: Drugs of the Future, (1994) 19/7 (656-658).
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L164 ANSWER 62 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92135798 EMBASE
DOCUMENT NUMBER: 1992135798
TITLE: Novel **acetylcholinesterase** inhibitors for treatment of cognitive disorders.
SOURCE: Current Opinion in Therapeutic Patents, (1992) 2/3 (281-283).
ISSN: 0962-2594 CODEN: COTPES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L164 ANSWER 63 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89098925 EMBASE
DOCUMENT NUMBER: 1989098925
TITLE: Heptylstigmine tartrate.
SOURCE: Drugs of the Future, (1989) 14/2 (123-124).
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

Searched by Barb O'Bryen, STIC 308-4291

L164 ANSWER 64 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-137877 [14] WPIDS
DOC. NO. CPI: C2001-040480
TITLE: Compositions for treating neurodegeneration and **cognitive** decline and **dysfunction** comprise a phytoestrogen or mammalian estrogen and an **acetylcholinesterase inhibitor** or their derivatives, analogues or metabolites.
DERWENT CLASS: B05
INVENTOR(S): ANTHONY, M; CLARKSON, T; NOTELOVITZ, M; PAN, Y
PATENT ASSIGNEE(S): (NOTE-I) NOTELOVITZ M; (UYWA-N) UNIV WAKE FOREST
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001000215	A1	20010104	(200114)*	EN	43

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001000215	A1	WO 2000-US17200	20000623

PRIORITY APPLN. INFO: US 1999-141189 19990625
AB WO 200100215 A UPAB: 20010312
NOVELTY - A composition for treating neurodegeneration and **cognitive** decline and **dysfunction** comprises a combination of a phytoestrogen and an **acetylcholinesterase inhibitor** or their derivatives, analogues or metabolites.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
(i) a composition for treating neurodegeneration and **cognitive** decline and **dysfunction** comprising a combination of a mammalian estrogen and an **acetylcholinesterase inhibitor** or their derivatives, analogues or metabolites;
(ii) a composition for treating neurodegeneration and **cognitive** decline and **dysfunction** comprises a combination of a phytoestrogen, a mammalian estrogen and an **acetylcholinesterase inhibitor** or their derivatives, analogues or metabolites;
(iii) a composition (and method) for enhancing **memory** and concentration in mammals comprising a combination of phytoestrogen and an **acetylcholinesterase inhibitor** or their derivatives, analogues or metabolites;
(iv) a method for improving **memory** and concentration in mammals comprising a combination of mammalian estrogen and an **acetylcholinesterase inhibitor** or their derivatives, analogues or metabolites;
(v) a soy-derived material in combination with an **acetylcholinesterase inhibitor** to improve **memory** and concentration in **animals**.
ACTIVITY - Nootropic; Neuroprotective.
MECHANISM OF ACTION - **Acetylcholinesterase inhibitor**; Estrogenic.
Searched by Barb O'Bryen, STIC 308-4291

USE - The composition is useful for treating neurodegeneration and **cognitive** decline and **dysfunction**, especially in normal cycling pre-perimenopausal women, menopausal women, post-menopausal women and those at risk of developing **memory** impairment. The composition is especially useful for treating conditions associated with Alzheimer's disease, ageing, other related dementia disorders and menopause.
Dwg.0/8

L164 ANSWER 65 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-524151 [47] WPIDS
DOC. NO. CPI: C2000-155612
TITLE: New pyrrolidine or piperidine derivatives, useful for enhancing cognition and for treatment of **memory** impairment in Alzheimer's disease, senile dementia and related conditions, are **acetylcholinesterase inhibitors**.
DERWENT CLASS: B02 B03
INVENTOR(S): REGAN, C M; SZMUSZKOVICZ, J
PATENT ASSIGNEE(S): (AMBI-N) AMERICAN BIOGENETIC SCI INC; (UYDU-N) UNIV COLLEGE DUBLIN
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000033788	A2	20000615	(200047)*	EN	31

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000021609 A 20000626 (200047)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000033788	A2	WO 1999-US28374	19991201
AU 2000021609	A	AU 2000-21609	19991201

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000021609	A	Based on	WO 200033788

PRIORITY APPLN. INFO: US 1998-111839 19981211
AB WO 200033788 A UPAB: 20000925
NOVELTY - Pyrrolidine or piperidine derivatives (I) and (II) are new.
DETAILED DESCRIPTION - Pyrrolidine or piperidine derivatives of formula (I) and (II) are new.
R1 = H, OH, halogen, alkoxy, CF3, CN, carboalkoxy, alkanoyl or alkylsulfonyl or optionally substituted alkyl, cycloalkyl, aryl, aralkyl, haloalkyl or haloalkoxy;
n = 1-4;
R2 = OR5 or NR6R7;
R3 = H, OH, halo, alkoxy, optionally substituted straight chain alkyl, branched alkyl, cycloalkyl, aryl, aralkyl, alkaryl, haloalkyl or haloalkoxy;
R5 = optionally substituted alkyl, cycloalkyl, aryl, aralkyl, alkaryl

or haloalkyl;
R6, R7 = H or optionally substituted alkyl, cycloalkyl, aryl, aralkyl, alkaryl, alkanoyl, aroyl, aralkanoyl or alkaroyl; or
NR6R7 = azetidine, morpholine, pyridine or piperidine;
Ra, Rb = H; or
Ra+Rb = O;
m = 1 or 2;
provided that:
(1) when R5 = alkyl, alkaryl or aralkyl, Ra and Rb = H;
(2) when one of R6 and R7 = aryl, Ra and Rb = H;
(3) when R5 = H, Ra and Rb = H; and
(4) when R6 and R7 = H, Ra and Rb = H.
p is not defined.
ACTIVITY - Nootropic.
Male Wistar rats were trained in a one-trial step-through light-dark passive avoidance paradigm where the dark compartment administered a 0.75 mA scrambled electric shock when the **animal** had all four paws in the dark area. The **animals** were tested for recall of this inhibitory stimulus by placing them in the light compartment and noting the time taken to enter the dark compartment.
1-Benzylpyrrolidine-2-(N-benzyl)carboxamide (Ia) at 30 mg/kg extended the latency to 447 plus or minus 106 seconds, compared with 559 plus or minus 28 seconds for saline controls, 544 plus or minus 61 seconds for (Ia) with scopolamine (0.8 mg/kg) and 52 plus or minus 12 seconds for scopolamine alone (scopolamine is used to induce **amnesia**).
MECHANISM OF ACTION - **Acetylcholinesterase inhibitor**.
USE - As **acetylcholinesterase inhibitors** to enhance cognition and for treatment of **memory** impairment in Alzheimer's disease, senile dementia and similar disorders.
ADVANTAGE - Avoids the toxicity problems associated with tacrine-type prior art drugs.
Dwg.0/0

L164 ANSWER 66 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-018005 [03] WPIDS
DOC. NO. CPI: C2001-005155
TITLE: Treatment of **age-related** behavior disorders and **memory** disorders in **companion animals** using acetyl cholinesterase inhibitor, especially 2,3-dihydro-benzo(d)isoxazole or 2,3-dihydro-benzo(d)isothiazole derivative.
DERWENT CLASS: B02 C02
INVENTOR(S): LUNDY, K M
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC
COUNTRY COUNT: 27
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1050303	A2	20001108	(200103)*	EN	11
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
CA 2306574	A1	20001027	(200103)	EN	
JP 2000309545	A	20001107	(200106)		11

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1050303	A2	EP 2000-303253	20000413

CA 2306574 A1 CA 2000-2306574 20000425
JP 2000309545 A JP 2000-114594 20000417

PRIORITY APPLN. INFO: US 1999-131243 19990427
AB EP 1050303 A UPAB: 20010116
NOVELTY - Method of treating an **age-related behavior** disorder, **inappropriate elimination**, **memory** loss, **disorientation** or **confusion** or improving the **cognitive process** or **social interactions** or adjusting the **sleep-wake** cycle in a **companion animal** comprising administering an **acetyl choline esterase inhibitor** (I).
ACTIVITY - Nootropic; neuroprotective; antidepressant.
MECHANISM OF ACTION - **Acetyl choline esterase inhibitor**.
USE - For treating an **age-related** behavior **disorder** (preferably **cognitive dysfunction** syndrome or involutive **depression**), **inappropriate elimination**, **memory** loss, **disorientation** or **confusion** or improving the **cognitive process** or **social interactions** or adjusting the **sleep-wake** cycle in a **companion animal**, preferably a **dog** or **cat**. Assays are described, but no results given.
Dwg.0/0

L164 ANSWER 67 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-205118 [17] WPIDS
DOC. NO. CPI: C1999-059744
TITLE: New huperzine A derivatives - used to treat Alzheimer's dementia, myasthenia gravis, **age related** memory impairment, Down's syndrome and glaucoma.
DERWENT CLASS: B02
INVENTOR(S): KOZIKOWSKI, A P; TUECKMANTEL, W
PATENT ASSIGNEE(S): (MACR-N) MACRO HI-TECH JV LTD
COUNTRY COUNT: 81
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9911625	A1	19990311	(199917)*	EN	50

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 9889259 A 19990322 (199931)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9911625	A1	WO 1998-US18260	19980902
AU 9889259	A	AU 1998-89259	19980902

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 9889259 A Based on WO 9911625

PRIORITY APPLN. INFO: US 1997-922734 19970903

AB WO 9911625 A UPAB: 19990503

NOVELTY - Huperzine A derivatives (I) are new. DETAILED DESCRIPTION - Huperzine A derivatives of formula (I) and their salts are new. X = O or S; Y = O, S, CH2, CH(R), C(R)(R), CH=CH, C(R)=CH, CH=C(R), C(R)=C(R), NH or N(R); p = 0-1; R = phenyl, 2-24C alkyl, 2-24C alkenyl, 2-24C alkynyl, 3-24C cycloalkyl, 3-24C cycloalkenyl, adamantyl, bicyclo(m.n.o)alkyl and all positional isomers of furyl, thienyl, quinolyl, isoquinolyl, indolyl, naphthyl, anthracenyl, biphenylyl, tetrahydronaphthyl, indanyl, phenanthrenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoxazolyl, isothiazolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl or morpholinyl (all optionally substituted by one or more halo, CF3, phenyl, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, OH, O-(1-8C) alkyl, O-(2-8C) alkenyl, O-(2-8C) alkynyl, OC(O)-(1-8C) alkyl, OC(O)-2-8C alkenyl, OC(O)-2-8C alkynyl, SH, S-(1-8C) alkyl, S-(2-8C) alkenyl, S-(2-8C) alkynyl, SC(O)-(1-8C) alkyl, SC(O)-2-8C alkenyl, SC(O)-2-8C alkynyl, CN, NO2, C(O)-1(1-8C) alkyl, C(O)-(2-8C) alkenyl, C(O)-(2-8C) alkynyl, CO2H, CO2-(1-8C) alkyl, CO2-(2-8C) alkenyl, CO2-(2-8C) alkynyl, NH2, NH-mono- or di-(1-8C) alkyl, NH3+, N+(tri-(1-8C) alkyl, C(O)NH2, C(O)NH(1-8C) alkyl, C(O)N-di-(1-8C) alkyl, S(O)-(1-8C) alkyl, S(O)-(2-8C) alkenyl, S(O)-(2-8C) alkynyl, SO3H, SO2-(1-8C) alkyl, SO2-(2-8C) alkenyl or SO2-(2-8C) alkynyl; m, n, o = 0-10; m + n + o = 2-24. and when p = 0 and X = O, C(=X)R can additionally be the C-terminus of an amino acid or peptide. Also included is an INDEPENDENT CLAIM for the preparation of (I).

USE - Used for treating Alzheimer's' dementia, myasthenia gravis, **age-related** memory impairment, Down's syndrome and glaucoma (claimed). (I) are used in humans or for veterinary use, e.g. **dogs**, particularly those used as guides for the sight impaired.

ACTIVITY - None given. MECHANISM OF ACTION - **Acetylcholinesterase** (AChE) **inhibitor**. (I) was incubated with excess AChE-free human plasma containing an esterase that converts (I) to huperzine A. An aliquot of the resulting incubation mixture was removed and its ability to inhibit AChE measured in 50 mM sodium phosphate containing 1 mM dithionitrobenzoic acid (pH 8.0) at 22 deg. C, using 1 mM acetylthiocholine as the substrate. Inhibition of AChE was achieved by diluting a stock solution of (I) (2-5 mM) into an enzyme solution (150-20 units of AChE/ml) in 50 mM sodium phosphate (pH 8.0) containing 0.01% bovine serum albumin) and measuring residual enzyme activity at various times. Plots of percent residual activity against time at each concentration were used to calculate the rate of inhibition (kon). Direct measurement of the rate constant of regeneration of enzyme activity (koff) was initiated by a greater than 10000 times dilution of huperzine A-inhibited AChE (2-4 mu M) to show that the rate of inhibition by residual initiator was negligible in the reactivation medium. The assay showed that (I), upon hydrolysis by plasma esterase, show AChE inhibition comparable to that obtained with huperzine A when tested under analogous conditions (Ki = 7-45 nM).

ADVANTAGE - (I) are more able to cross the blood-brain barrier (BBB) than huperzine A and are relatively more effective at **inhibiting acetylcholinesterase**. (I) are retained in circulation in the body and reside in brain depots for longer periods until hydrolysed by enzymes to release huperzine A. Combination of enhanced transversal and brain residence properties leads to longer duration of action of huperzine A, reducing the number of daily doses required. Improved delivery to the brain reduces the incidence and severity of undesirable side-effects of huperzine A administration, such as dizziness and nausea.

Dwg.0/0

L164 ANSWER 68 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
Searched by Barb O'Bryen, STIC 308-4291

ACCESSION NUMBER: 1995-302470 [39] WPIDS
DOC. NO. CPI: C1995-135370
TITLE: Treating mammalian dementia using new and known pyridinium derivs. - which selectively **inhibit acetylcholinesterase** and which are nerve agent antidotes.
DERWENT CLASS: B03
INVENTOR(S): BUCCAFUSCO, J J; POWERS, J C; STARKS, K M
PATENT ASSIGNEE(S): (GEOR-N) GEORGIA TECH RES CORP
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9521822	A1	19950817	(199539)*	EN	83
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9513383	A	19950829	(199548)		
US 5714615	A	19980203	(199812)		36
US 5726314	A	19980310	(199817)		30

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9521822	A1		WO 1994-US14220	19941209
AU 9513383	A		AU 1995-13383	19941209
US 5714615	A		US 1994-193217	19940208
US 5726314	A	Div ex	US 1994-193217	19940208
			US 1996-723293	19960930

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9513383	A	Based on	WO 9521822

PRIORITY APPLN. INFO: US 1994-193217 19940208; US 1996-723293 19960930

AB WO 9521822 A UPAB: 19951004
Treating mammalian dementia comprises admin. of a pyridinium deriv. of formula (I), (II) or (III) and any counter ion to make salts: Xa = X and Xb and Xc = H; or Xa = H; Xb = X1 and Xc = B; Z = 1-6C alkyl, opt. substd. by 1-2 opt. substd. phenyl or naphthyl; X = OH, 1-6C alkylNHCO2, (1-6C alkyl)2NCO2, 1-6C fluoroalkylNHCO2 or (1-6C fluoroalkyl)2NHCO2; Y = O or S; R2 = H, opt. substd. 1-6C alkyl, pentafluorophenyl, opt. substd. phenyl, 1-6C alkyl-(opt. substd. phenyl), or naphthyl; R3, R8 = H, 1-6C alkyl, opt. substd. phenyl, pentafluorophenyl or 1-6C alkyl-(opt. substd. phenyl); B = H or 1-6C alkyl; Xd = X' and Xe, Xc = H; or Xd = H, Xe = X' and Xc = B; R4 = opt. substd. 1-6C alkyl; q' = 3-8; R', R'', R''' = H, 1-6C alkyl, 1-6C fluoroalkyl, 1-6C alkyl-(opt. substd. phenyl) or 1-6C fluoroalkyl-(opt. substd. phenyl); R7 = R2 with the exception of H. (I) are new where R2 = pentafluorophenyl, naphthyl or opt. substd. phenyl. Also claimed are pyridinium derivs. of formula (IV'): R5' = pentafluorophenyl, opt. substd. phenyl or naphthyl; R6' = H, 1-6C alkyl, opt. substd. phenyl, pentafluorophenyl or (1-6C alkyl)-(opt. substd. phenyl).
The cpds. selectively **inhibit acetylcholinesterase** and are useful as nerve agent antidotes and prophylactics. Certain unspecified quat. pyridinium derivs. offer in vivo protection against the nerve agents Somon and Tabun and other organophosphate poisons. They are also useful to treat e.g. myasthenia gravis, Alzheimer's disease,

presenile dementia of the Alzheimer type, Korsakoff's syndrome, **age-related** memory impairment, multi-infarct dementia, Parkinsonian dementia, Down's syndrome and postraumatic dementia.

(I) are different from other centrally acting AChE inhibitors used to treat Alzheimer's patients in that the molecules retain a permanent positive charge and may stimulate cholinergic receptors as well as inhibit esterase. (I) have enhanced hydrophobicity allowing them to cross the blood-brain barrier. (I) also stimulate nicotinic and/or nuxarinic receptors in the CNS.

Dwg.0/0

L164 ANSWER 69 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1991-165984 [23] WPIDS
DOC. NO. CPI: C1991-071824
TITLE: New 4-amino-quinoline derivs. with fused heterocyclic ring - are **acetyl-choline esterase inhibitors** for treating senile dementia and Alzheimer's disease.
DERWENT CLASS: B02
INVENTOR(S): FUJIWARA, H; KUROKI, Y; NAKAMURA, I; NISHINO, S; TOKUNAGA, H
PATENT ASSIGNEE(S): (UBEI) UBE IND LTD; (UBEI) UBE INDUSTRIES KK
COUNTRY COUNT: 4
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 430485	A	19910605	(199123)*		
R: DE FR GB					
JP 03220189	A	19910927	(199145)		
EP 430485	A3	19920122	(199322)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 430485	A	EP 1990-312392	19901113
JP 03220189	A	JP 1990-322393	19901128
EP 430485	A3	EP 1990-312392	19901113

PRIORITY APPLN. INFO: JP 1989-307591 19891129
AB EP 430485 A UPAB: 19931115
Quinoline derivatives of formula (I) and their acid addition salts are new. R1, R2 = H, halo, lower alkyl, CF3, OH, lower alkoxy, lower alkanoyloxy, NO2, NH2 or lower alkanoylamino; R3 = H, 1-15C alkyl, cycloalkyl, 7-15C aralkyl (optionally substituted by halo, lower alkyl or lower alkoxy, NO2, OH or NH2); n = 2-5.

Specifically claimed (I) are e.g. 4-amino-1-methyl-2,3-dihydro -1H-pyrrolo(2,3-b)quinoline, 5-amino-8-chloro-1- (m-methoxybenzyl) -1,2,3,4-tetrahydrobenzo(b)(1,8)-napthylidine and 5-amino-8-chloro-1- (m-hydroxybenzyl)-1,2,3,4-tetrahydrobenzo(b)(1,8)napthylidine. Dose is 0.1-1000 (1-500) mg/day.

USE/ADVANTAGE - (I) **inhibit acetylcholine esterase** by acting on central neurons and show beneficial effects on learning and **memory** tasks in amnesiac model **animals**. (I) are used for the prophylaxis and treatment of senile dementia and Alzheimer's disease and have low toxicity. @(31pp Dwg.No.0/0)@
0/0

L164 ANSWER 70 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1988-148729 [22] WPIDS

DOC. NO. CPI: C1988-066202
TITLE: New fused tri - and tetra cyclic derivs. of 4-amino-quinoline cpds. - useful in treating alzheimer's disease and senile dementia.
DERWENT CLASS: B02
INVENTOR(S): KAWAKAMI, H; KITANO, M; OHUCHI, R; ONO, K
PATENT ASSIGNEE(S): (SUMU) SUMITOMO PHARM CO LTD
COUNTRY COUNT: 15
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 268871	A	19880601	(198822)*	EN	73
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
JP 63166881	A	19880711	(198833)		
DK 8705690	A	19880501	(198837)		
JP 63225358	A	19880920	(198843)		
JP 63239271	A	19881005	(198846)		
JP 63264485	A	19881101	(198849)		
JP 64000073	A	19890105	(198907)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 268871	A	EP 1987-116008	19871030
JP 63166881	A	JP 1986-310931	19861229
JP 63225358	A	JP 1987-119686	19870515
JP 63239271	A	JP 1987-119687	19870515
JP 63264485	A	JP 1987-119685	19870515
JP 64000073	A	JP 1987-276238	19871031

PRIORITY APPLN. INFO: JP 1986-261579 19861031; JP 1986-261580 19861031; JP 1986-262983 19861105; JP 1986-310930 19861229; JP 1986-310931 19861229; JP 1987-78483 19870330; JP 1987-119685 19870515; JP 1987-119686 19870515; JP 1987-119687 19870515

AB EP 268871 A UPAB: 19930923
4-Aminoquinoline derivs. of formula (I) and pharmaceutically acceptable acid addn. salts are new, where (1) fused ring A = opt. alkyl substd. fused cyclopentane (a), cyclohexane (b) or cycloheptane (c) ring; R5, R6, R7 = H or lower alkyl; R1 = lower alkyl, halogen, CF3, NO2, NH2, OH, lower alkylamino, lower alkanoylamino, lower alkylthio, lower alkoxy or lower alkoxymethyl; R2, R3 = H, halogen, lower alkyl, lower alkoxy, lower cycloalkyl, or opt. substd. phenyl; and R4 = H; provided that when R1 = lower alkyl, lower alkoxy, Cl, Br or I, and R2=R3=H; provided that when R1 = lower alkyl, lower alkoxy, Cl, Br or I, and R2=R3=H, then ring A = (a) or (c) where R5, R7 = lower alkyl; or (2) ring A = gp. of formula (d)-(i) where n, q, r, s = 1 or 2; p = 0 or 1; each X,Y = bond or opt. substd. alkylene, provided X+Contains 1-3C; R8-26 = H or lower alkyl; R1-3 = H, halogen, CF3, NO2, NH2, OH, lower alkyl, lower alkoxy, lower alkylamino, lower alkanoylamino, lower cycloalkyl, lower alkylthio, lower alkoxymethyl, or opt. substd. phenyl; and R4 = H, lower alkyl, aralkyl or diaralkyl.
USE/ADVANTAGE - (I) are **acetylcholinesterase inhibitors** which increase brain acetylcholine levels, and have strong activity in amnestic models in several **animals** without adverse side effects. (I) are thus useful in treating **memory** dysfunctions, e.g. Alzheimer's disease and senile dementia. Adult doses are e.g. 1-500, pref. 5-300 mg/day, opt. divided.

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L164 ANSWER 71 OF 71 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1986-120308 [19] WPIDS
DOC. NO. CPI: C1986-051187
TITLE: New 4-aryl-1,2,4-triazole-5-carbamate derivs. - useful as **acetyl-choline esterase inhibitors**, e.g. for treating Alzheimers disease.
DERWENT CLASS: B03
INVENTOR(S): ENSINGER, H; FROLKE, W; HINZEN, D; KUHN, F J; LEHR, E; TROGER, W; WALTHER, G; WEBER, K H
PATENT ASSIGNEE(S): (BOEH) BOEHRINGER INGELHEIM
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 180115	A	19860507	(198619)*	GE	28
R: AT BE CH DE FR GB IT LI LU NL SE					
DE 3439450	A	19860507	(198620)		
AU 8549094	A	19860501	(198625)		
JP 61103876	A	19860522	(198627)		
NO 8504276	A	19860320	(198627)		
FI 8504178	A	19860428	(198636)		
DK 8504913	A	19860428	(198640)		
DD 236928	A	19860625	(198643)		
PT 81370	A	19861105	(198650)		
HU 40091	T	19861128	(198701)		
ES 8701738	A	19870301	(198715)		
ES 8704468	A	19870616	(198729)		
ZA 8508195	A	19870427	(198729)		
CS 8507593	A	19870716	(198734)		
CS 8604625	A	19870716	(198735)		
US 4732900	A	19880322	(198815)		
CA 1244030	A	19881101	(198848)		
SU 1429934	A	19881007	(198916)		
SU 1436873	A	19881107	(198922)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 180115	A	EP 1985-113278	19851019
DE 3439450	A	DE 1984-3439450	19841027
JP 61103876	A	JP 1985-236563	19851024
ES 8701738	A	ES 1985-548206	19851025
ES 8704468	A	ES 1986-554373	19860425
ZA 8508195	A	ZA 1985-8195	19851025
US 4732900	A	US 1985-791184	19851025
SU 1429934	A	SU 1986-4028478	19861111
SU 1436873	A	SU 1985-3965776	19851022

PRIORITY APPLN. INFO: DE 1984-3439450 19841027
AB EP 180115 A UPAB: 19930922
Triazolo-carbamates of formula (I) and their physiologically acceptable acid addn. salts are new. R1 = H, 1-8C alkyl, 3-6 membered carbocyclic ring, benzyl or phenethyl; R2 = phenyl or pyridyl, opt. substd. by 1 or 2 of halo, Me, MeO or CF3; R3 and R4 = H, 1-6C alkyl, 3-6C cycloalkyl or aryl or heteroaryl, both opt. substd. by halo, MeO, CF3 or 1-6C alkyl; or together they complete a satd. 5-6 membered ring opt. substd. by 1 or more 1-4C alkyl and opt. contg. an additional N, O or S heteroatom, which if N

can be substd. by 1-4C alkyl or 1-3C hydroxyalkyl.

USE - (I) are **inhibitors** of **acetylcholine esterase**. In **animal** tests they show (1) improvements in CNS, cortical wakening reaction; (2) increases in the proportion of REM sleep; (3) activation of the discharge frequency of central cholinergic nerve cells; (4) improvements in learning and **memory** performance; (5) improvements in the short time/long time **memory** index after admin. of muscarin cholinergic antagonists. (I) are of low toxicity, have no peripheral side effects and are useful in treatment of Alzheimer type senile dementia.

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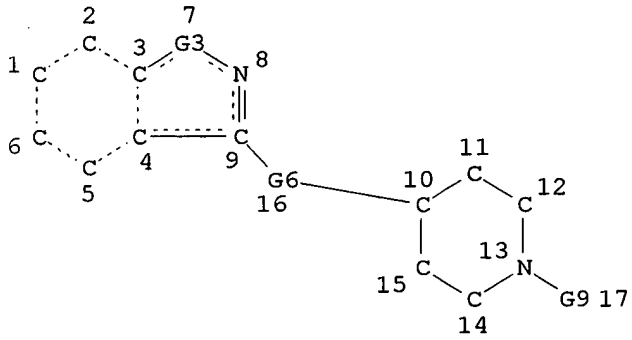
Structure of claim 10



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Ak @36

CH=CH @23 @24

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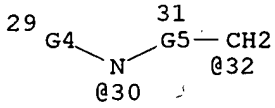

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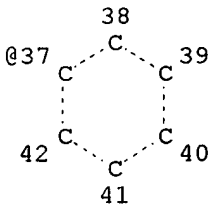
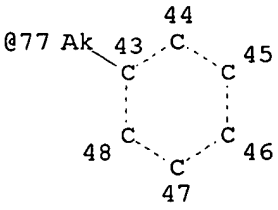
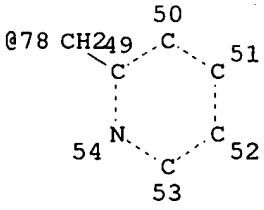
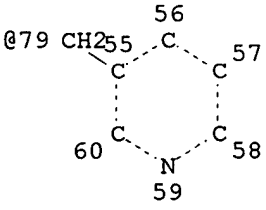
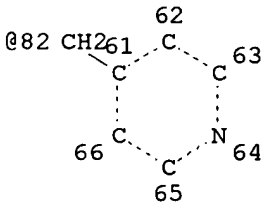


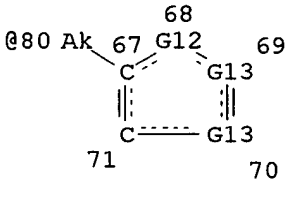


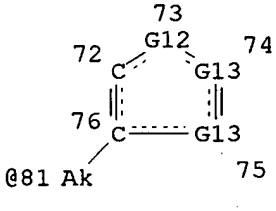




Page 1-A







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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 20 Mar 2001 (20010320/PD)
FILE LAST UPDATED: 20 Mar 2001 (20010320/ED)
HIGHEST PATENT NUMBER: US8345926
CA INDEXING IS CURRENT THROUGH 20 Mar 2001 (20010320/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 20 Mar 2001 (20010320/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2000
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2000

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>>> is included in file records.  A thesaurus is available for the  <<<
>>> USPTO Manual of Classifications in the /NCL, /INCL, and /RPCL   <<<
>>> fields.  This thesaurus includes catchword terms from the       <<<
>>> USPTO/MOC subject headings and subheadings.  Thesauri are also  <<<
>>> available for the WIPO International Patent Classification      <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4,     <<<
>>> /IC5, and /IC (/IC6) fields, respectively.  The thesauri in     <<<
>>> the /IC5 and /IC fields include the corresponding catchword     <<<
>>> terms from the IPC subject headings and subheadings.            <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L165            STR
L167        128 SEA FILE=REGISTRY SSS FUL L165
L169          4 SEA FILE=USPATFULL ABB=ON  L167

=> dup rem l168,l169

FILE 'CAPLUS' ENTERED AT 16:34:49 ON 20 MAR 2001
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FILE 'USPATFULL' ENTERED AT 16:34:49 ON 20 MAR 2001
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L168
PROCESSING COMPLETED FOR L169
L171         21 DUP REM L168 L169 (3 DUPLICATES REMOVED)
                ANSWERS '1-20' FROM FILE CAPLUS
                ANSWER '21' FROM FILE USPATFULL

=> d ibib abs hitstr l171 1-21; fil cao; d que nos l170
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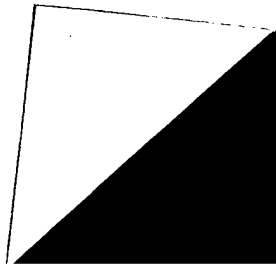
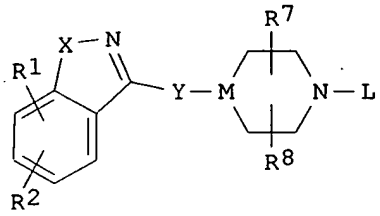


L171 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 1998:306974 CAPLUS
DOCUMENT NUMBER: 129:4661
TITLE: Preparation of benzisoxazoles and benzisothiazoles as cholinesterase inhibitors
INVENTOR(S): Villalobos, Anabella; Nagel, Arthur A.; Chen, Yuhpyng L.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 33 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5750542	A	19980512	US 1993-127847	19930928
US 5538984	A	19960723	US 1995-445814	19950522

PRIORITY APPLN. INFO.: US 1993-127847 19930928
OTHER SOURCE(S): MARPAT 129:4661
GI



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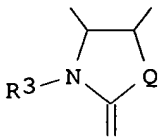

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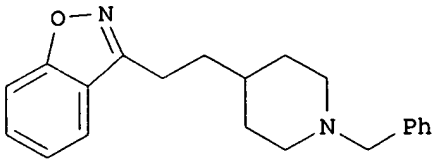


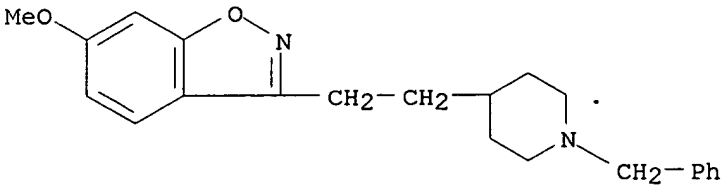
III

AB The title compds. [I; R1 and R2 are attached to adjacent carbon atoms and form, together with the carbon atoms to which they are attached, a group II (wherein J = O, S, NR4; R4 = H, C1-4 alkyl; R3 = H, C1-6 alkyl; Q = (CH2)t; T = 1); R1, R2 = H, OH, PhO, etc.; X = O, S; Y = (CH2)m, O(CH2)m, CH:CH(CH2)n, NR4(CH2)m (n = 0-3; m = 1-2); M = CH; L = (un)substituted Ph, phenyl-(C1-6 alkyl), cinnamyl, pyridylmethyl; R7, R8 = H, C1-6 alkyl, C1-6 alkoxy, etc.] and their salts, useful in enhancing memory in patients suffering from dementia and Alzheimer's disease, were prepd. Thus, 5-step synthesis of the title compd. III.maleate, starting from Et isonipecotate, was described. Compds. I are effective at 0.01-1 mg/day for the av. adult human.

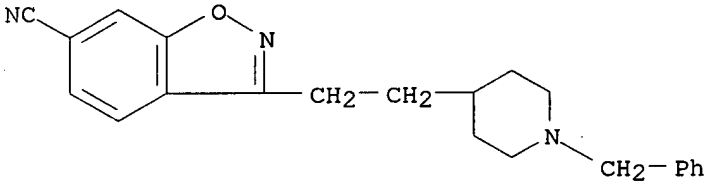
IT **145508-55-0P 145508-58-3P 145508-74-3P**
145508-75-4P 145508-78-7P 145815-96-9P
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)
(prepn. of benzisoxazoles and benzisothiazoles as cholinesterase inhibitors)

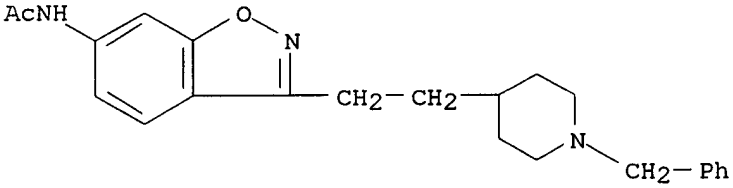
RN 145508-55-0 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



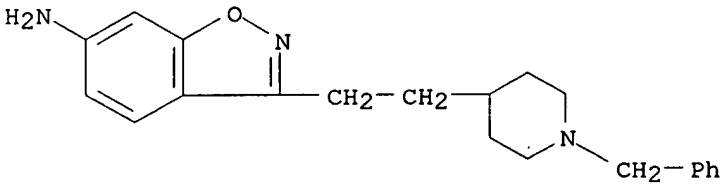
RN 145508-58-3 CAPLUS
CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



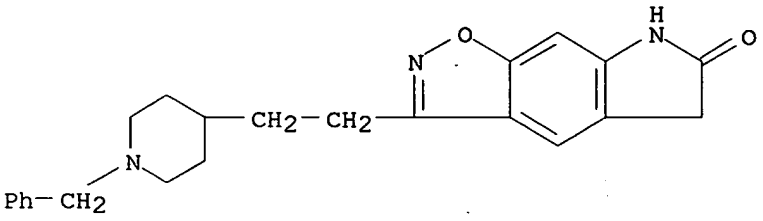
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



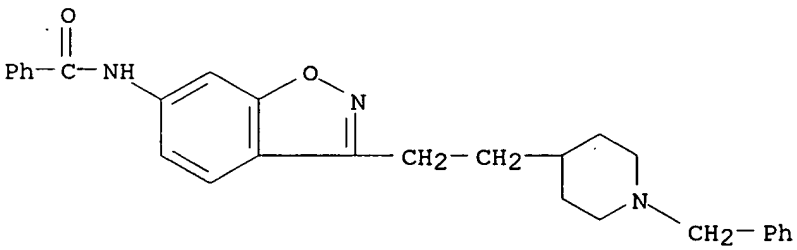
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-96-9 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

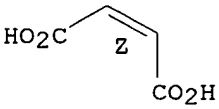
CRN 145508-76-5
CMF C28 H29 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



IT **145508-56-1P 145508-57-2P 145508-59-4P**
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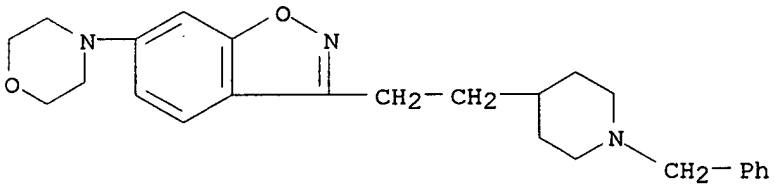
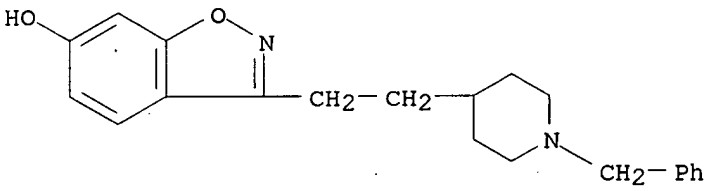
145508-67-4P 145508-68-5P 145508-69-6P
145508-70-9P 145508-71-0P 145508-72-1P
145508-76-5P 145508-77-6P 145508-80-1P
145508-82-3P 145508-83-4P 145508-84-5P
145508-85-6P 145508-87-8P 145508-88-9P
145815-88-9P 145815-89-0P 145815-90-3P
145815-91-4P 145815-92-5P 145815-93-6P
145815-94-7P 145815-95-8P 145815-97-0P
145815-98-1P 145816-00-8P 145816-02-0P
145816-03-1P 145816-04-2P 145816-05-3P
145816-07-5P 145816-08-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic
Searched by Barb O'Bryen, STIC 308-4291

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzisoxazoles and benzisothiazoles as cholinesterase inhibitors)

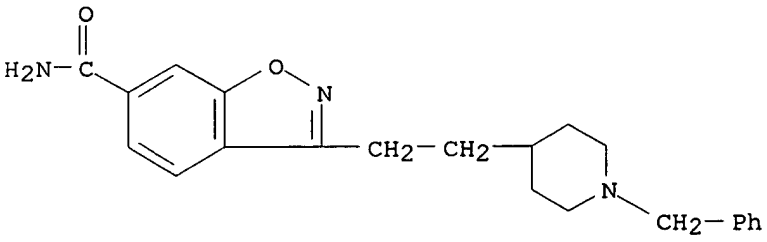
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



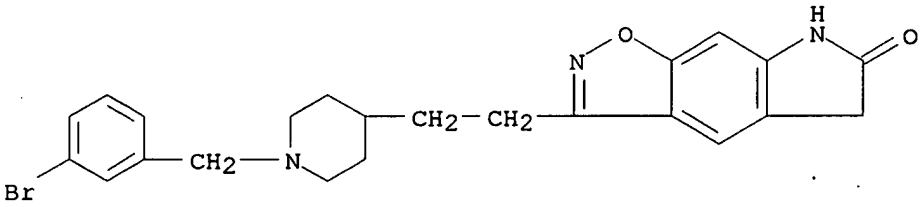
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

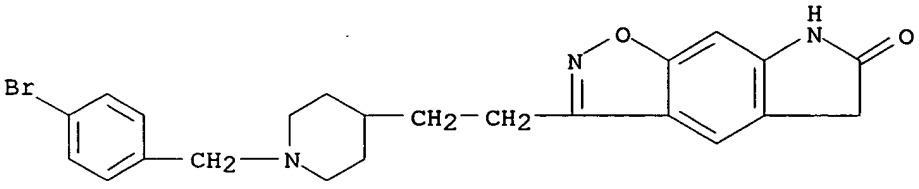


RN 145508-64-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(3-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)

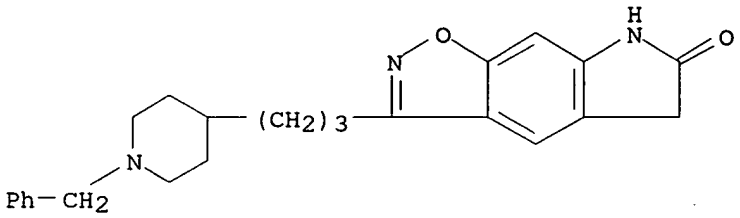


Searched by Barb O'Bryen, STIC 308-4291

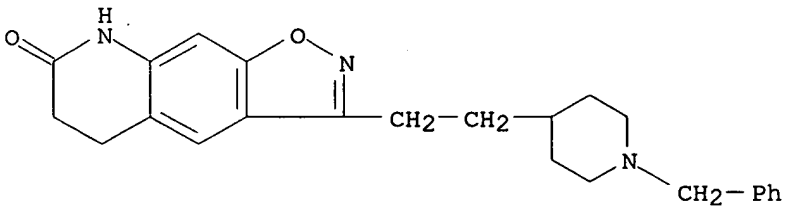
RN 145508-65-2 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(4-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)



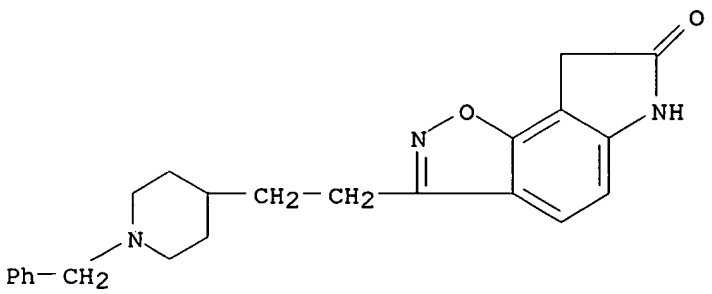
RN 145508-66-3 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



RN 145508-67-4 CAPLUS
CN Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



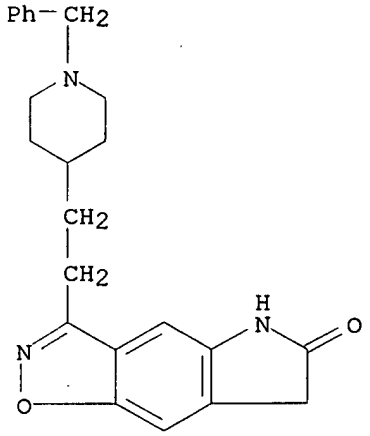
RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



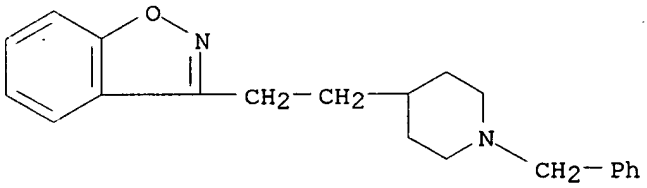
RN 145508-69-6 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

CN 6H-Pyrrolo[2,3-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-71-0 CAPLUS
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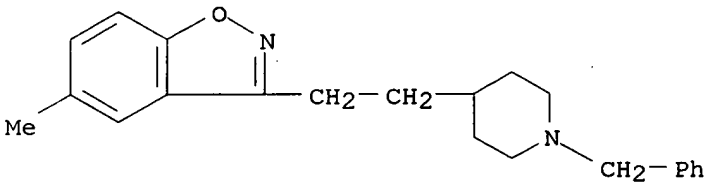

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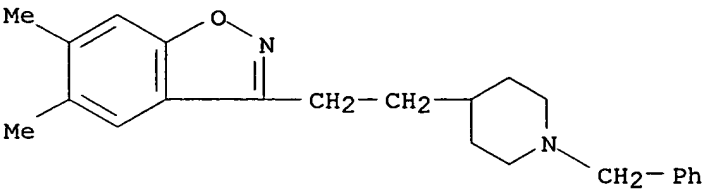
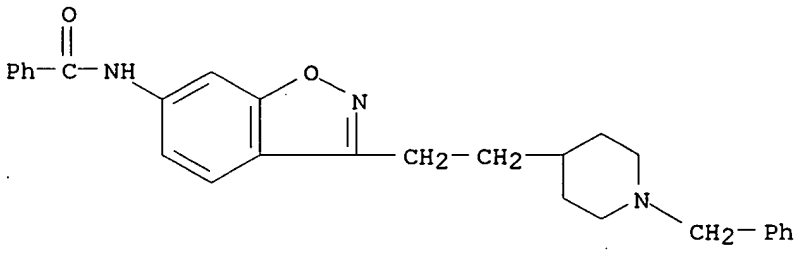
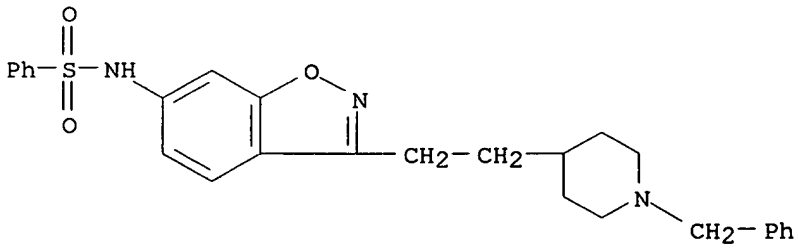
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 145508-80-1 CAPLUS
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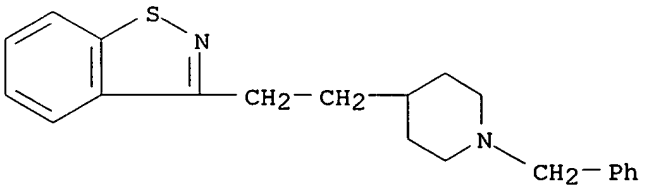

RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

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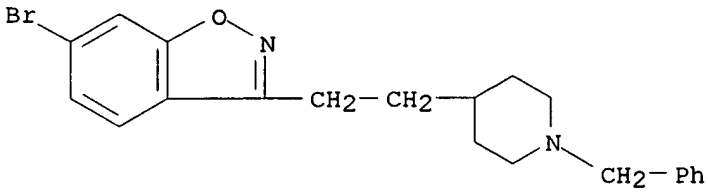

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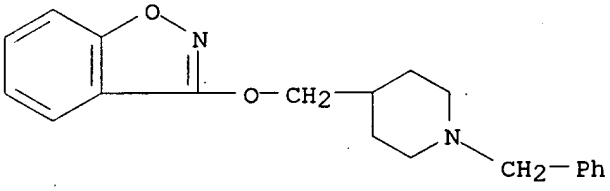

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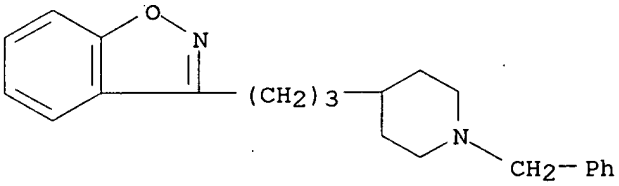

RN 145508-85-6 CAPLUS
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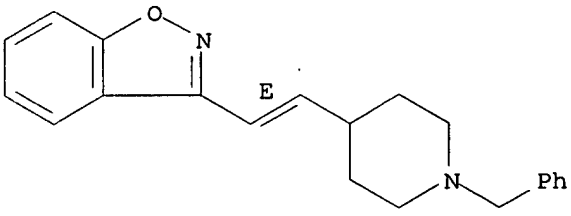
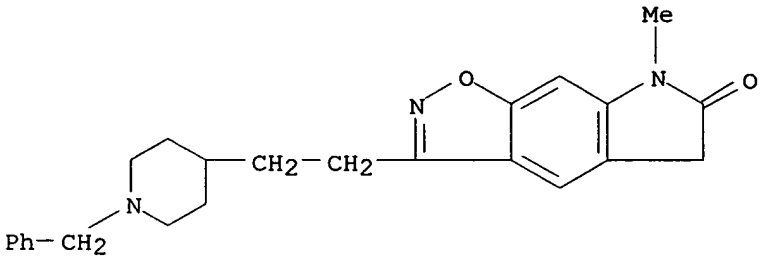
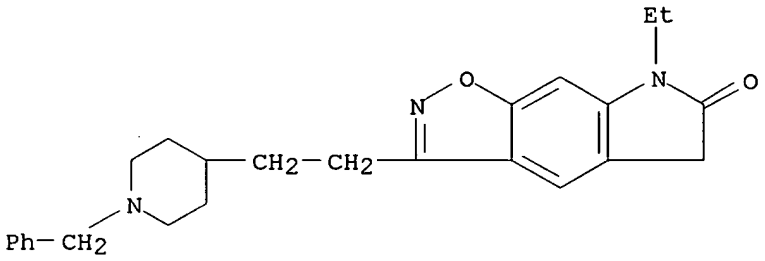
Double bond geometry as shown.



RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



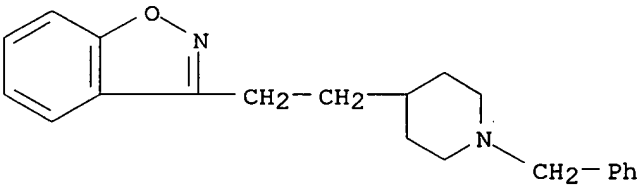
RN 145508-88-9 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-88-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

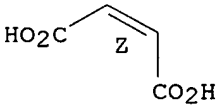
CRN 145508-70-9
CMF C21 H24 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

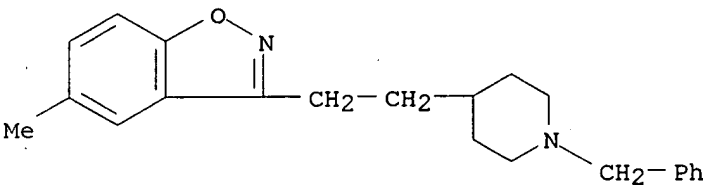
Double bond geometry as shown.



RN 145815-89-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

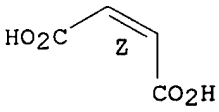
CRN 145508-71-0
CMF C22 H26 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

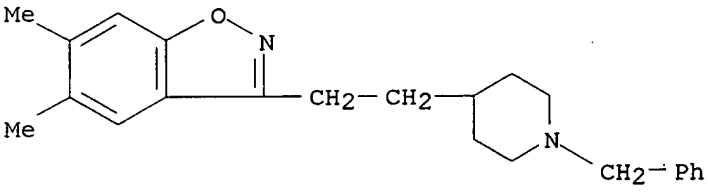
Double bond geometry as shown.



RN 145815-90-3 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

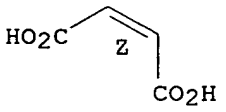
CRN 145508-72-1
CMF C23 H28 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

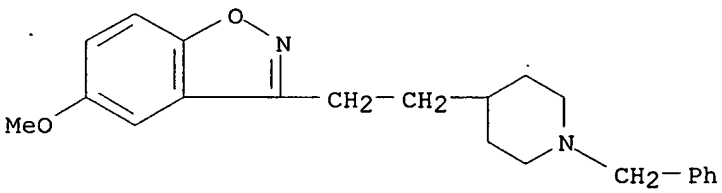
Double bond geometry as shown.



RN 145815-91-4 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

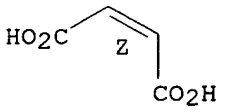
CRN 145508-73-2
CMF C22 H26 N2 O2



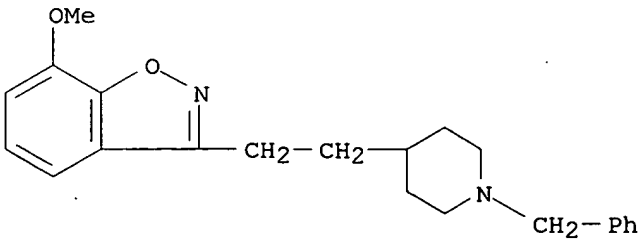
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



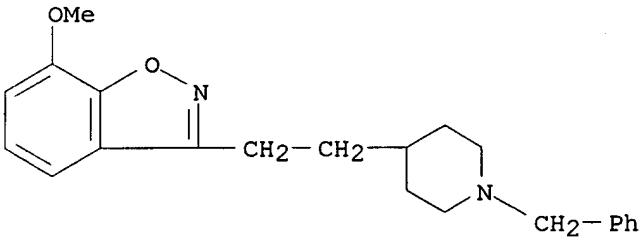
RN 145815-92-5 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-93-6 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

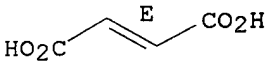
CRN 145815-92-5
CMF C22 H26 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

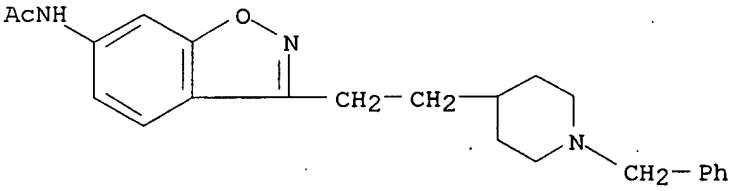
Double bond geometry as shown.



RN 145815-94-7 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

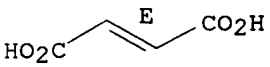
CRN 145508-74-3
CMF C23 H27 N3 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.

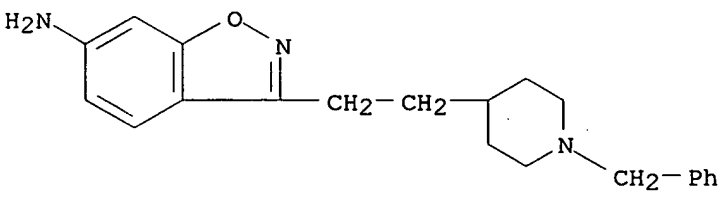


RN 145815-95-8 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-,

(2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

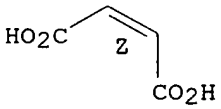
CRN 145508-75-4
CMF C21 H25 N3 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

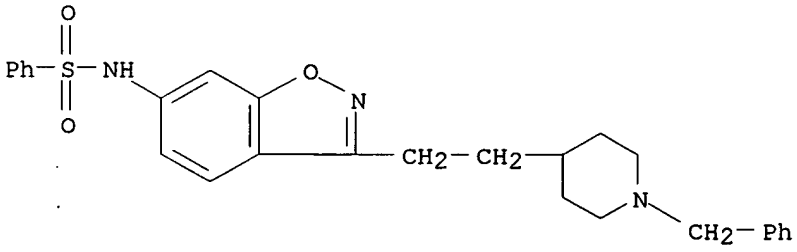
Double bond geometry as shown.



RN 145815-97-0 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

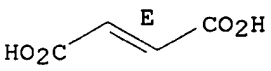
CRN 145508-77-6
CMF C27 H29 N3 O3 S



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

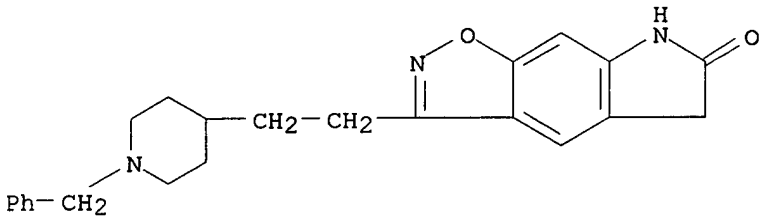
Double bond geometry as shown.



RN 145815-98-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

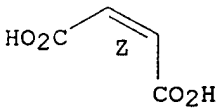
CRN 145508-78-7
CMF C23 H25 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

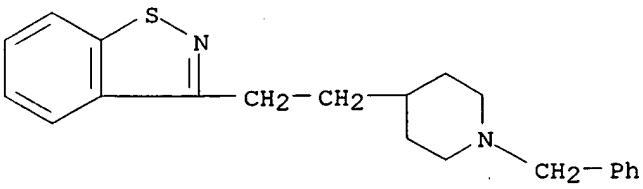
Double bond geometry as shown.



RN 145816-00-8 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

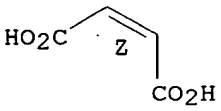
CRN 145508-80-1
CMF C21 H24 N2 S



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

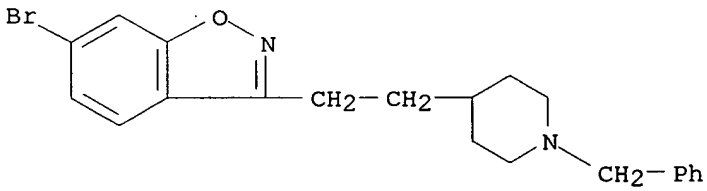
Double bond geometry as shown.



RN 145816-02-0 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

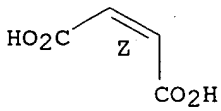
CRN 145508-82-3
CMF C21 H23 Br N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

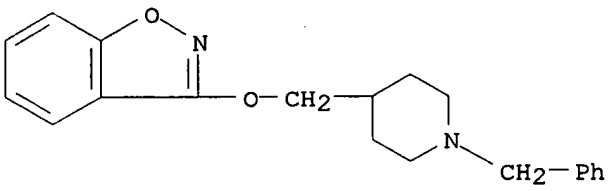
Double bond geometry as shown.



RN 145816-03-1 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

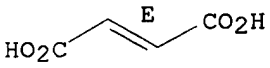
CRN 145508-83-4
CMF C20 H22 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

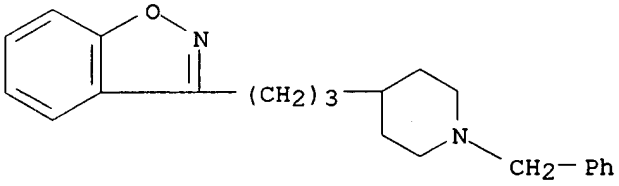
Double bond geometry as shown.



RN 145816-04-2 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

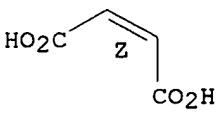
CRN 145508-84-5
CMF C22 H26 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

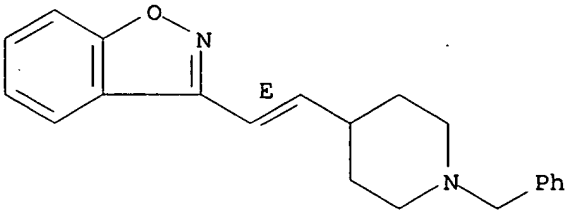


RN 145816-05-3 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-85-6
CMF C21 H22 N2 O
CDES 2:E

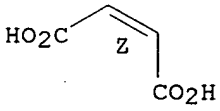
Double bond geometry as shown.



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

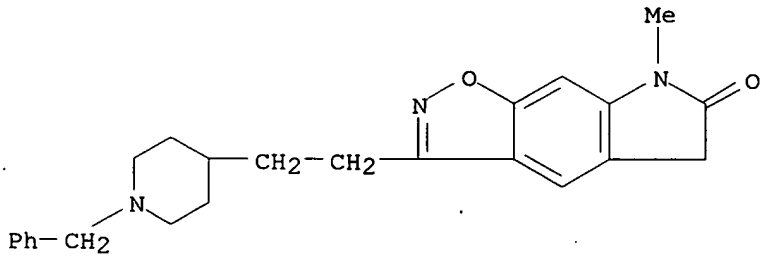
Double bond geometry as shown.



RN 145816-07-5 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

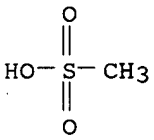
CM 1

CRN 145508-87-8
CMF C24 H27 N3 O2



CM 2

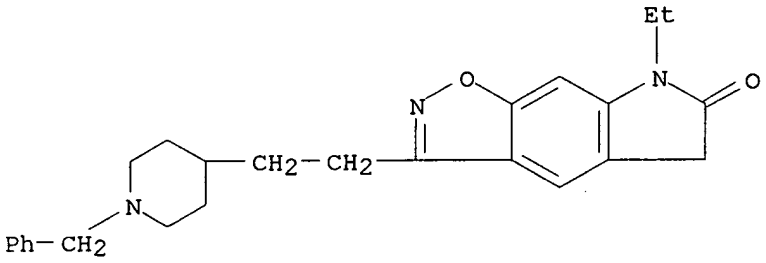
CRN 75-75-2
CMF C H4 O3 S



RN 145816-08-6 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

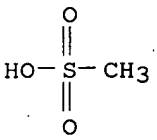
CM 1

CRN 145508-88-9
CMF C25 H29 N3 O2



CM 2

CRN 75-75-2
CMF C H4 O3 S



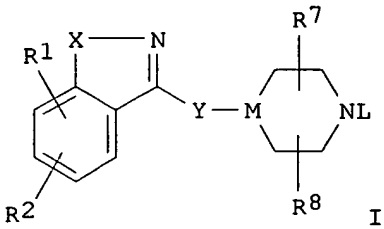
L171 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 1996:527733 CAPLUS
DOCUMENT NUMBER: 125:195639
TITLE: Methods of using piperidyl-benzisoxazole and benzisothiazole derivatives as cholinesterase inhibitors
INVENTOR(S): [redacted] Villalobos, Anabella; Nagel, Arthur A.; Chen, Yuhpyng L.
PATENT ASSIGNEE(S): [redacted] Pfizer Inc., USA
SOURCE: U.S., 33 pp. Division of U.S. Ser. No. [redacted] 127,847.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 5538984	A	19960723	US 1995-445814	19950522
US 5750542	A	19980512	US 1993-127847	19930928
PRIORITY APPLN. INFO.:			US 1993-127847	19930928

OTHER SOURCE(S): MARPAT 125:195639

GI



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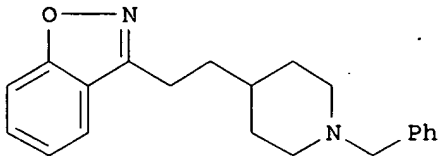


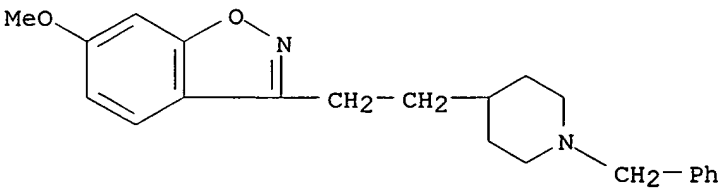
III

AB The invention relates to compds. I [R1, R2 = H, OH, alkoxy, (un)substituted PhCH2O, PhO, Ph, or PhCH2, halo, NO2, nitro, cyano, (un)substituted amino, etc.; or R1R2 may form certain heterocyclic rings; X = O, S, CH:CH, CH:N, N:CH, N:N, NR4; R4 = H, alkyl; Y = (CH2)m, CH:CH(CH2)n, NR4(CH2)m, or O(CH2)m; n = 0-3 and m = 1-3; M = CH or N; L = (un)substituted Ph, phenylalkyl, cinnamyl, pyridylmethyl, or sidechains contg. other 5-membered arom. heterocycles; R7, R8 = H, alkyl, alkoxycarbonyl, alkylcarbonyl, alkoxy, with the proviso that alkoxy is not attached to a C which is adjacent to N]. I are cholinesterase inhibitors, useful for enhancing memory in patients suffering from dementia and Alzheimer's disease (no data). Examples include 36 syntheses of I plus various salts and intermediates. For instance, Et isonipecotate underwent N-BOC protection (94%), redn. of the ester with LiAlH4 to give the (hydroxymethyl) analog (93%), and conversion of this to the (iodomethyl) analog, i.e. 4-(iodomethyl)-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (II) (92%). Then, 3-methyl-1,2-benzisoxazole was .alpha.-lithiated with LiN(Pr-iso)2 and coupled with II (42%), followed by deprotection and N-benzylation (73%) to give title compd. III, which was converted to its maleate (87%).

IT **145508-55-0P 145508-58-3P 145508-74-3P 145508-75-4P 145508-78-7P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperidyl-contg. benzisoxazole and benzisothiazole derivs. as cholinesterase inhibitors)

RN 145508-55-0 CAPLUS

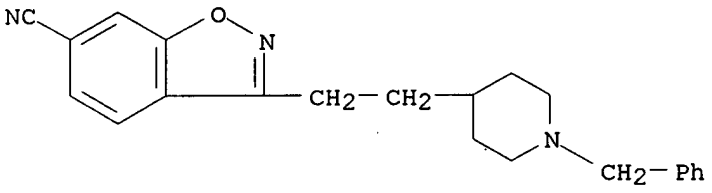
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



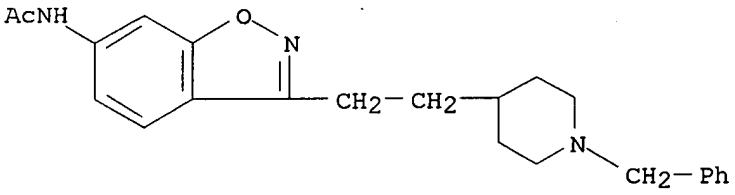
RN 145508-58-3 CAPLUS

CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

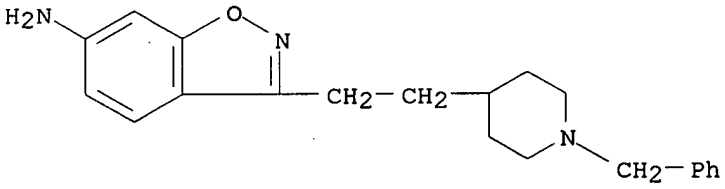
Searched by Barb O'Bryen, STIC 308-4291



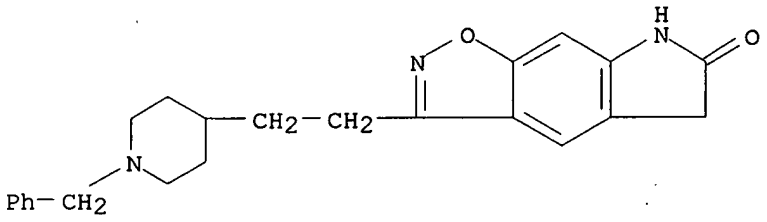
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



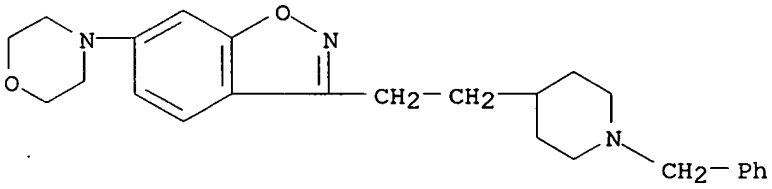
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



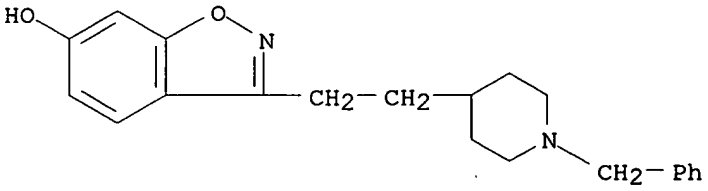
IT **145508-56-1P 145508-57-2P 145508-59-4P**
145508-64-1P 145508-65-2P 145508-66-3P
145508-67-4P 145508-68-5P 145508-69-6P
145508-70-9P 145508-71-0P 145508-72-1P
145508-73-2P 145508-76-5P 145508-77-6P
145508-80-1P 145508-82-3P 145508-83-4P
145508-84-5P 145508-85-6P 145508-87-8P
145508-88-9P 145815-88-9P 145815-89-0P

145815-90-3P 145815-91-4P 145815-92-5P
145815-93-6P 145815-94-7P 145815-95-8P
145815-96-9P 145815-97-0P 145815-98-1P
145816-00-8P 145816-02-0P 145816-03-1P
145816-04-2P 145816-05-3P 145816-07-5P
145816-08-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperidyl-contg. benzisoxazole and benzisothiazole derivs. as cholinesterase inhibitors)

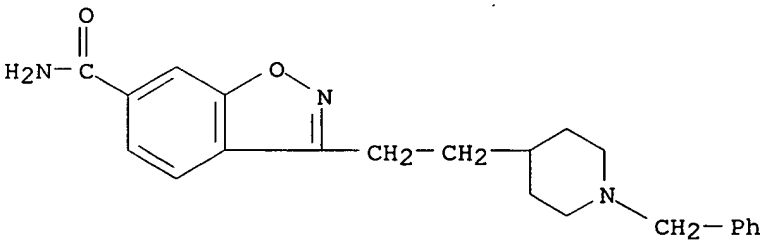
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



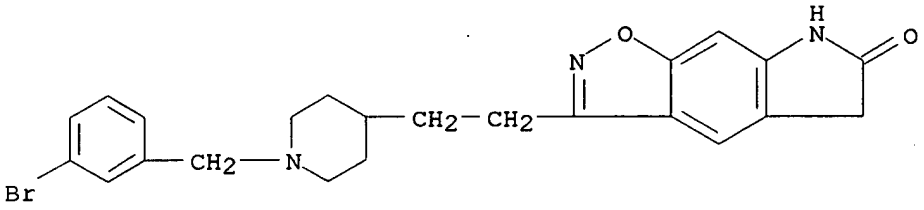
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



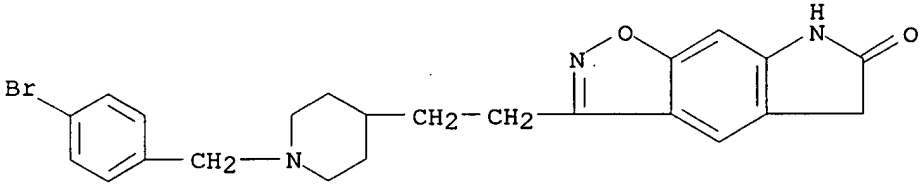
RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



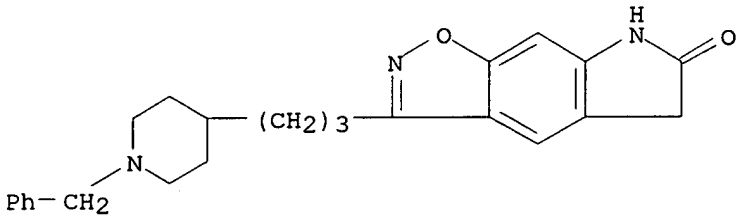
RN 145508-64-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(3-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)



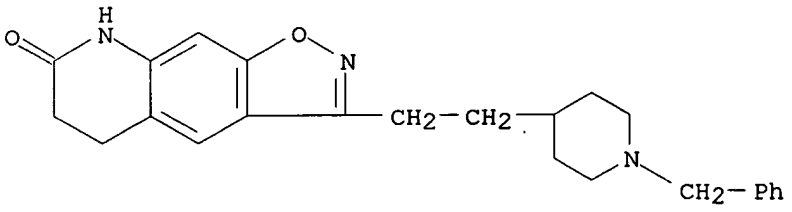
RN 145508-65-2 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(4-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)



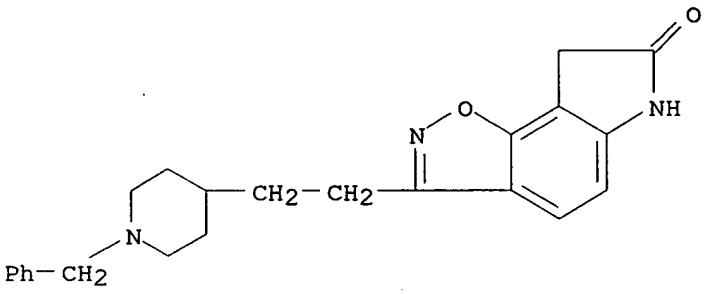
RN 145508-66-3 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



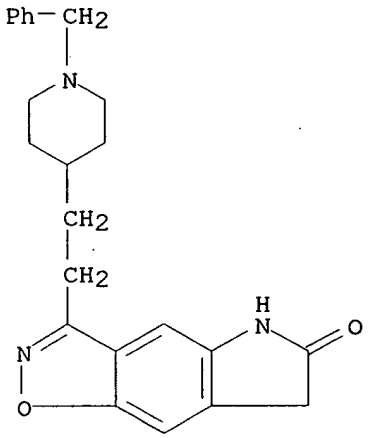
RN 145508-67-4 CAPLUS
CN Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



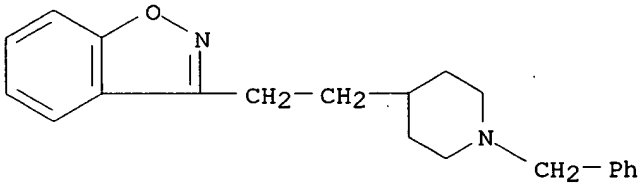
RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



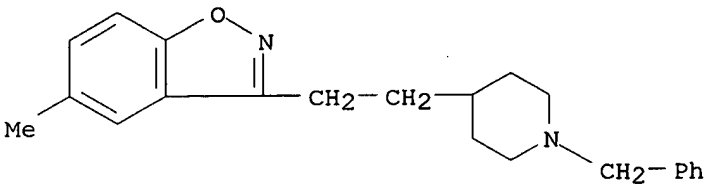
RN 145508-69-6 CAPLUS
CN 6H-Pyrrolo[2,3-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



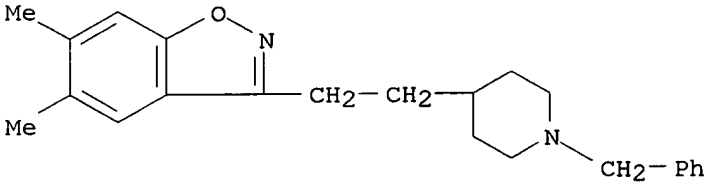
RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



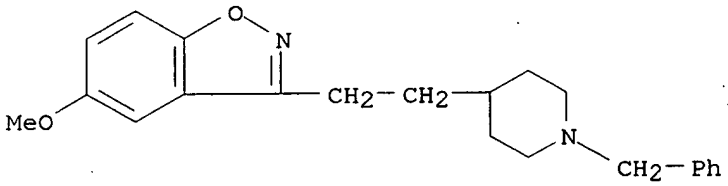
RN 145508-71-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



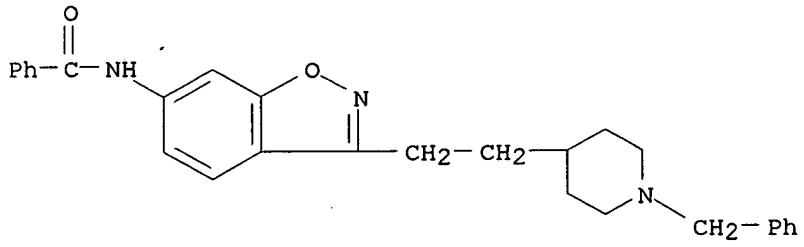
RN 145508-72-1 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



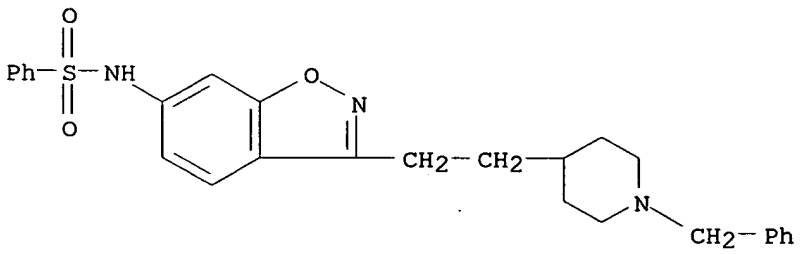
RN 145508-73-2 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



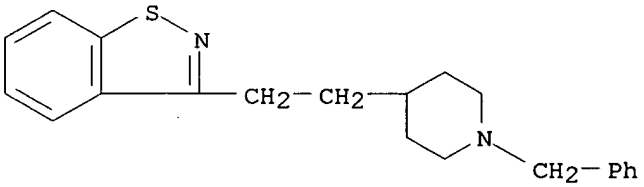
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



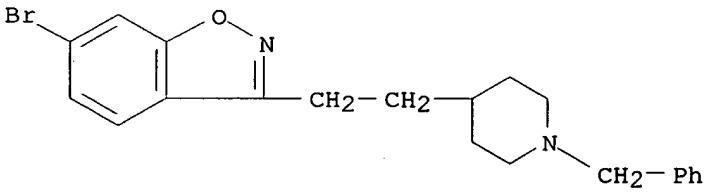
RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



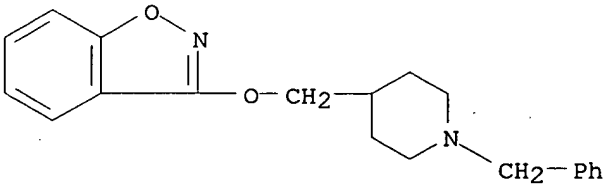
RN 145508-80-1 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



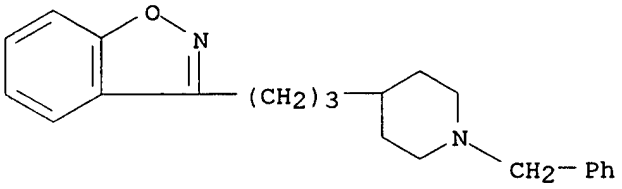
RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-83-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]- (9CI) (CA INDEX NAME)

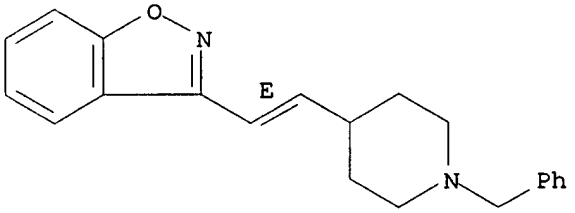


RN 145508-84-5 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)

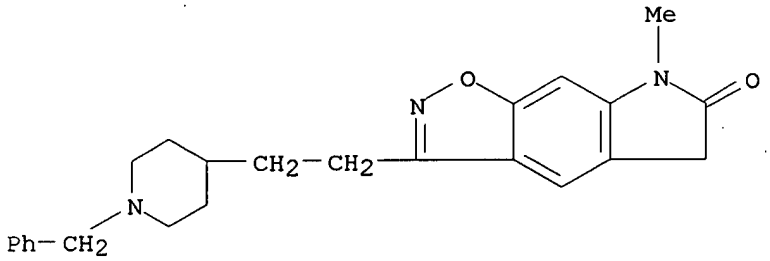


RN 145508-85-6 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]- (9CI) (CA INDEX NAME)

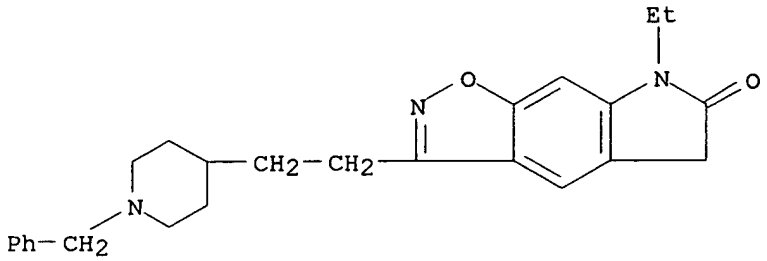
Double bond geometry as shown.



RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-88-9 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

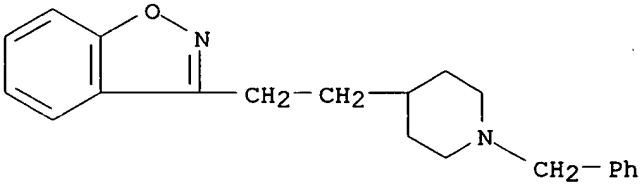


RN 145815-88-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

CM 1

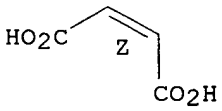
CRN 145508-70-9
CMF C21 H24 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

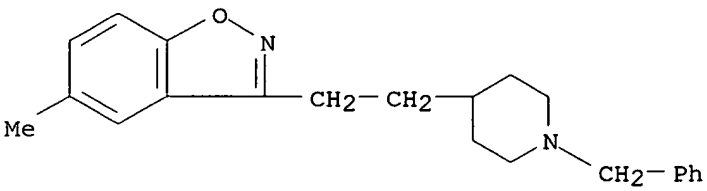
Double bond geometry as shown.



RN 145815-89-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

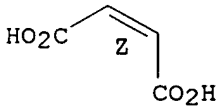
CRN 145508-71-0
CMF C22 H26 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

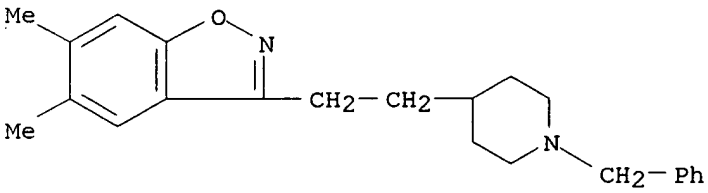
Double bond geometry as shown.



RN 145815-90-3 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

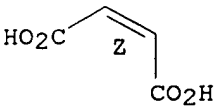
CRN 145508-72-1
CMF C23 H28 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

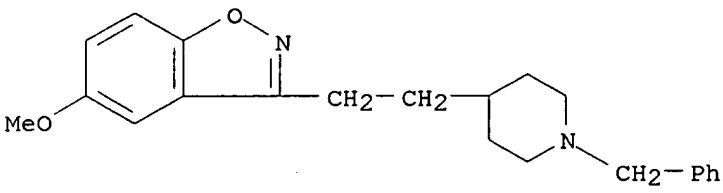
Double bond geometry as shown.



RN 145815-91-4 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

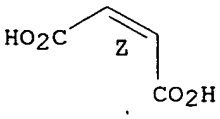
CRN 145508-73-2
CMF C22 H26 N2 O2



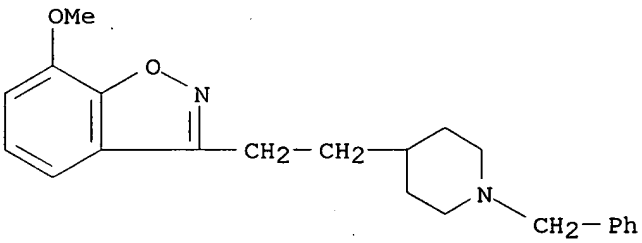
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



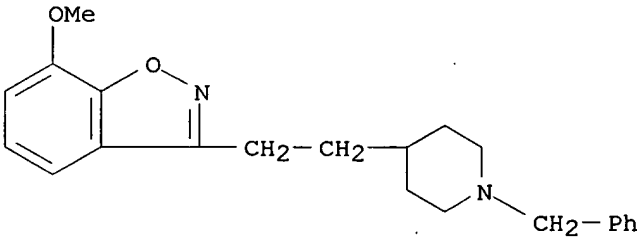
RN 145815-92-5 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-
(9CI) (CA INDEX NAME)



RN 145815-93-6 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-,
(2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

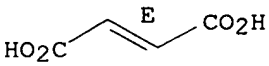
CRN 145815-92-5
CMF C22 H26 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

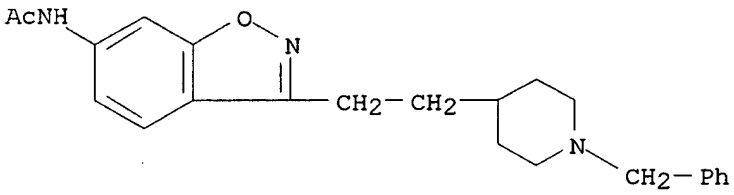
Double bond geometry as shown.



RN 145815-94-7 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

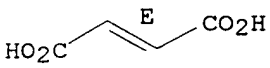
CRN 145508-74-3
CMF C23 H27 N3 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

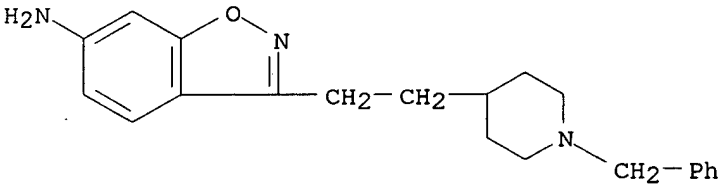
Double bond geometry as shown.



RN 145815-95-8 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

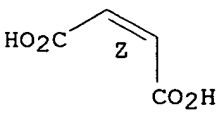
CRN 145508-75-4
CMF C21 H25 N3 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

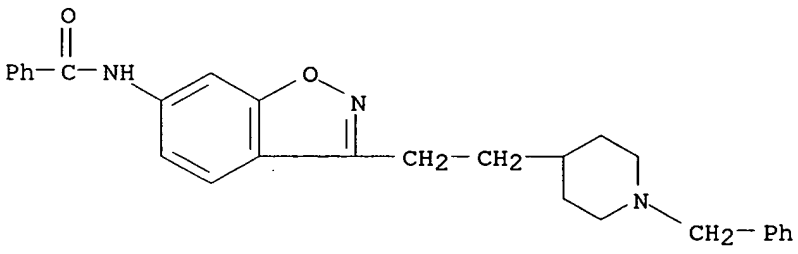
Double bond geometry as shown.



RN 145815-96-9 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

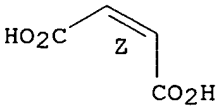
CRN 145508-76-5
CMF C28 H29 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

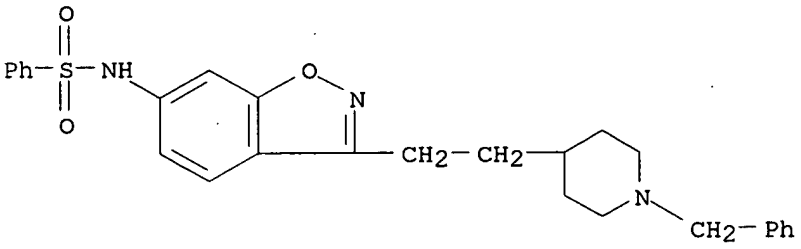
Double bond geometry as shown.



RN 145815-97-0 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

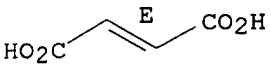
CRN 145508-77-6
CMF C27 H29 N3 O3 S



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

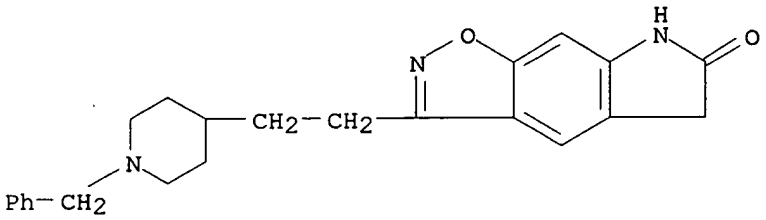
Double bond geometry as shown.



RN 145815-98-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

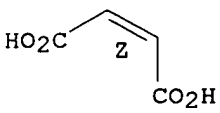
CRN 145508-78-7
CMF C23 H25 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

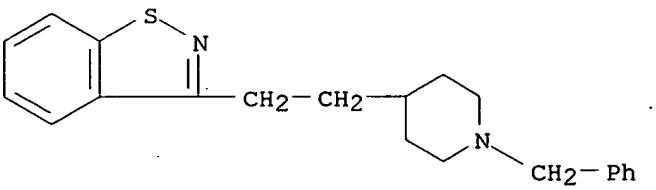


RN 145816-00-8 CAPLUS

CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

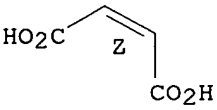
CRN 145508-80-1
CMF C21 H24 N2 S



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

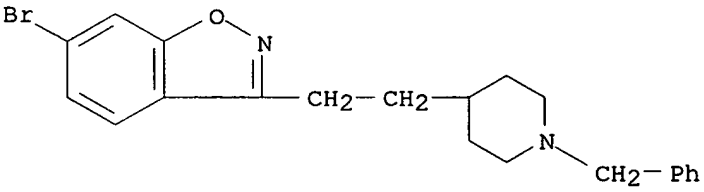
Double bond geometry as shown.



RN 145816-02-0 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

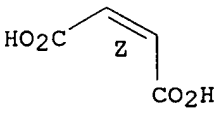
CRN 145508-82-3
CMF C21 H23 Br N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

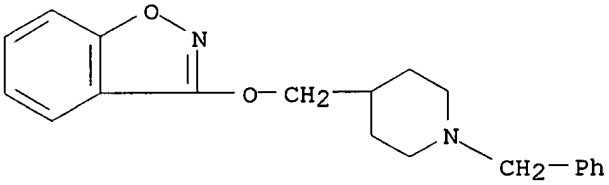
Double bond geometry as shown.



RN 145816-03-1 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

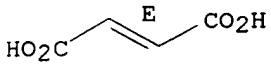
CRN 145508-83-4
CMF C20 H22 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

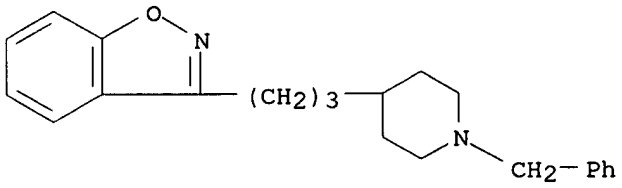
Double bond geometry as shown.



RN 145816-04-2 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-84-5
CMF C22 H26 N2 O

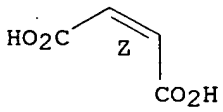


CM 2

CRN 110-16-7

CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

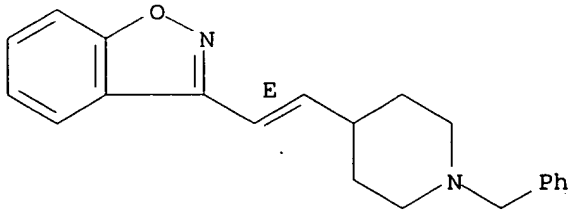


RN 145816-05-3 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-85-6
CMF C21 H22 N2 O
CDES 2:E

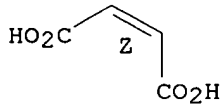
Double bond geometry as shown.



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

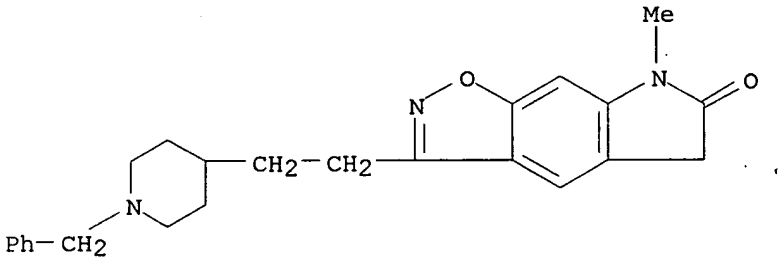
Double bond geometry as shown.



RN 145816-07-5 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

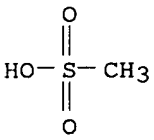
CM 1

CRN 145508-87-8
CMF C24 H27 N3 O2



CM 2

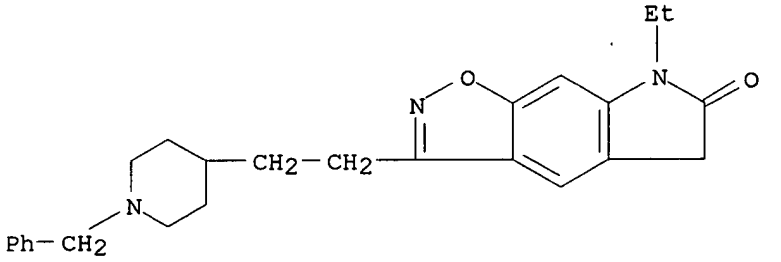
CRN 75-75-2
CMF C H4 O3 S



RN 145816-08-6 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

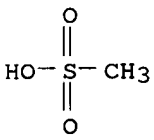
CM 1

CRN 145508-88-9
CMF C25 H29 N3 O2



CM 2

CRN 75-75-2
CMF C H4 O3 S

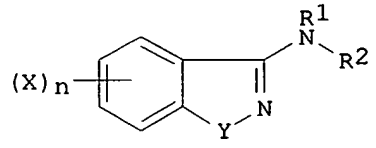


L171 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 1996:191579 CAPLUS
DOCUMENT NUMBER: 124:343282
TITLE: Substituted 3-(aminoalkylamino)-1,2-benzisoxazoles and related compounds useful as antidepressants
INVENTOR(S): O'Malley, Gerard J.; Palermo, Mark G.
PATENT ASSIGNEE(S): Hoechst-Roussel Pharmaceutical Incorporated, USA
SOURCE: U.S., 40 pp., Cont.-in-part of U. S. Ser. No.980,021, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

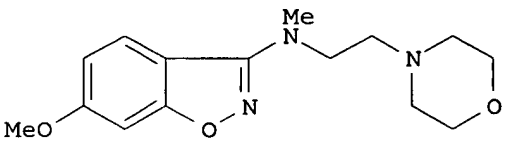
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5494908	A	19960227	US 1993-150301	19931112
CA 2149918	AA	19940609	CA 1993-2149918	19931122
WO 9412495	A1	19940609	WO 1993-US11416	19931122
W: AU, CA, FI, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 669920	A1	19950906	EP 1994-902374	19931122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08506094	T2	19960702	JP 1993-513352	19931122
FI 9502481	A	19950522	FI 1995-2481	19950522
NO 9502018	A	19950522	NO 1995-2018	19950522
US 5580982	A	19961203	US 1995-470520	19950606
US 6046203	A	20000404	US 1995-471197	19950606
US 5925766	A	19990720	US 1997-816817	19970318
US 5756754	A	19980526	US 1997-878876	19970619

PRIORITY APPLN. INFO.:
US 1992-980021 19921123
US 1993-150301 19931112
WO 1993-US11416 19931122
US 1995-469278 19950606
US 1995-470393 19950606

OTHER SOURCE(S): MARPAT 124:343282
GI



I



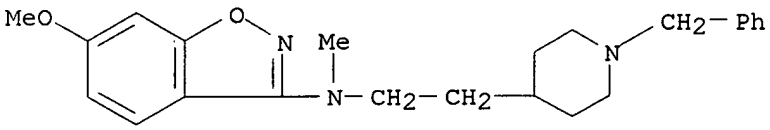
II

AB Title compds. I [R1 = H, alkyl, aralkyl, alkoxycarbonyl, (di)(alkyl)aminocarbonyl, etc.; X = H, alkyl, alkoxy, halo, (un)substituted OH or NH2; Y = O, S, (un)substituted NH; R2 = (CH2)m-Am where Am = (thio)morpholino, (un)substituted NH2, piperidinyl, pyridyl, piperazino; or NR1R2 forms cyclic amine; m = 2-7; n = 0-3] and their

pharmaceutically acceptable addn. salts, optical and geometric isomers, and racemic mixts. are disclosed. The compds. are useful for treatment of various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease. The compds. also inhibit monoamine oxidase (MAO), and are useful as antidepressants. For example, 3-chloro-6-methoxy-1,2-benzisoxasole and N-methyl-N-[2-(4-morpholinyl)ethyl]amine were condensed by heating together in a sealed tube at 140.degree. for 48 h to give title compd. II. In assays for inhibition of rat mitochondrial MAO (types A and B) in vitro, II had IC50 values of 13 and >103 .mu.M, vs. 0.18 and 23 for the std. brofaromine.

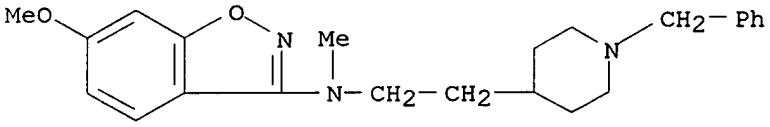
IT **176672-55-2P 176672-56-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (aminoalkylamino)benzisoxazoles as antidepressants and cholinomimetics)

RN 176672-55-2 CAPLUS
CN 1,2-Benzisoxazol-3-amine, 6-methoxy-N-methyl-N-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, hydrochloride (2:3) (9CI) (CA INDEX NAME)



●3/2 HCl

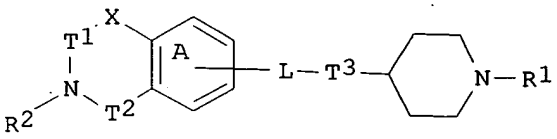
RN 176672-56-3 CAPLUS
CN 1,2-Benzisoxazol-3-amine, 6-methoxy-N-methyl-N-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



L171 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:277975 CAPLUS
DOCUMENT NUMBER: 132:308254
TITLE: Preparation of heterocyclic compounds as thermogenesis accelerators
INVENTOR(S): Ishihara, Yuji; Fujisawa, Yukio; Furuyama, Naoki; Ishichi, Yuji; Sasaki, Mitsuru
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 260 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000023437 A1 20000427 WO 1999-JP5705 19991015
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9961236 A1 20000508 AU 1999-61236 19991015
JP 2000186088 A2 20000704 JP 1999-293493 19991015
JP 2000186091 A2 20000704 JP 1999-293649 19991015
PRIORITY APPLN. INFO.: JP 1998-295213 19981016
JP 1998-295488 19981016
WO 1999-JP5705 19991015
OTHER SOURCE(S): MARPAT 132:308254
GI



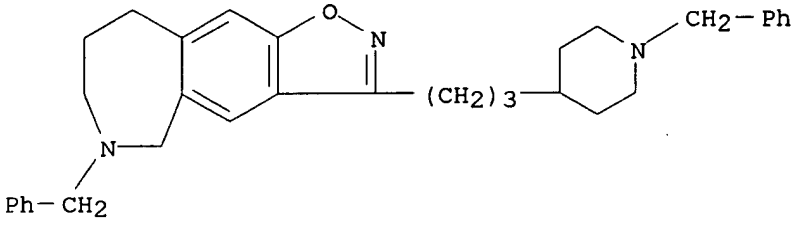
I

AB The title compds. I [T1 = (CH2)k; T2 = (CH2)m; T3 = (CHR)n; A is a benzene ring which may be further substituted; L is O, S or the like; n is an integer of 0 to 6; R is hydrogen, optionally substituted hydrocarbyl, or the like; R1 is optionally substituted hydrocarbyl, etc.,; R2 is hydrogen, acyl or the like; X is O, S, etc.; and k and m are each independently a no. of 0 to 5 and satisfy the relationship: 1 < k + m < 5] are prepd. I are useful in the treatment of obesity. The concn. of cAMP in fat cells in the presence of 7-[2-[1-(phenylmethyl)-4-piperidinyl]ethoxy]-3-(phenylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride (10-6 M) was 46.7 pmol/mL, vs. 2.7 pmol/mL in control fat cells. (Thermogenesis is increased when the concn. of cAMP in fat cells is increased). Formulations are given.

IT **265102-86-1P 265102-87-2P 265102-88-3P**
265102-89-4P 265102-90-7P 265102-91-8P
265102-92-9P 265102-93-0P 265102-94-1P
265103-15-9P 265103-16-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic compds. as thermogenesis accelerators)

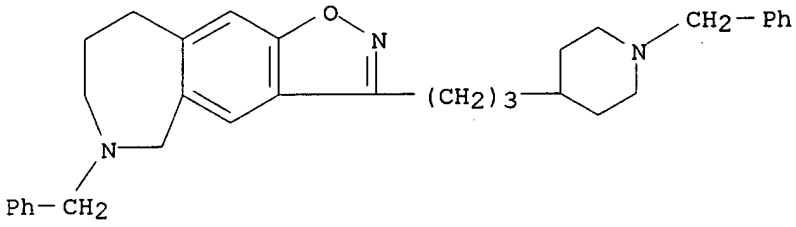
RN 265102-86-1 CAPLUS

CN 5H-Isoxazolo[5,4-h][2]benzazepine, 6,7,8,9-tetrahydro-6-(phenylmethyl)-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, dihydrochloride (9CI) (CA INDEX NAME)

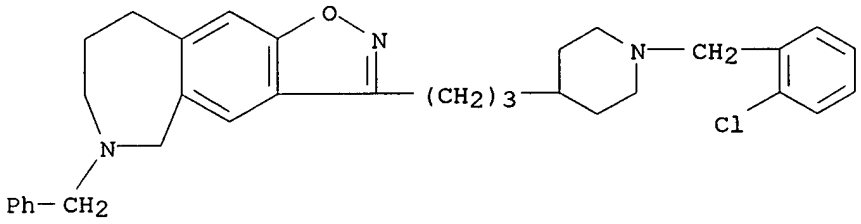


●2 HCl

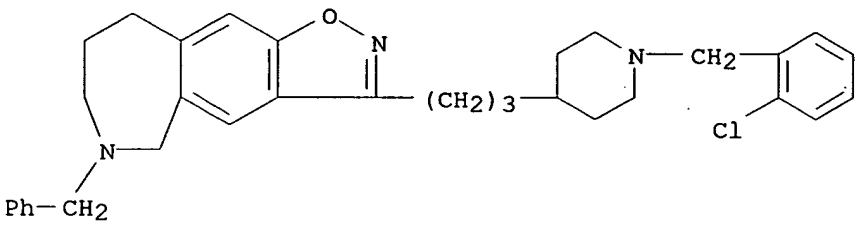
RN 265102-87-2 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 6,7,8,9-tetrahydro-6-(phenylmethyl)-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



RN 265102-88-3 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 3-[3-[1-[(2-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-6-(phenylmethyl)- (9CI) (CA INDEX NAME)

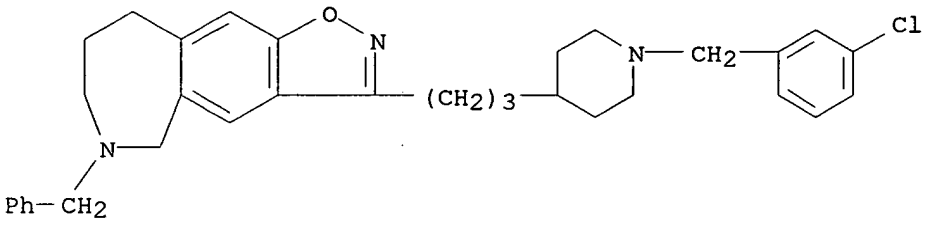


RN 265102-89-4 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 3-[3-[1-[(2-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-6-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)



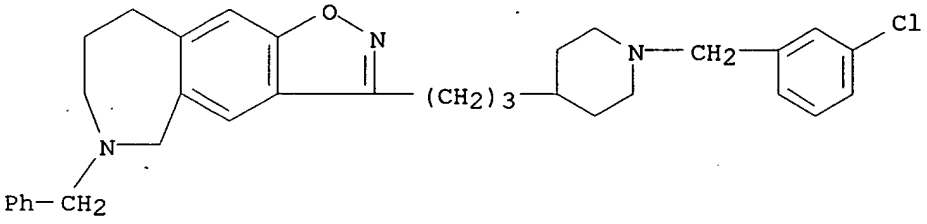
●2 HCl

RN 265102-90-7 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 3-[3-[1-[(3-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-6-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

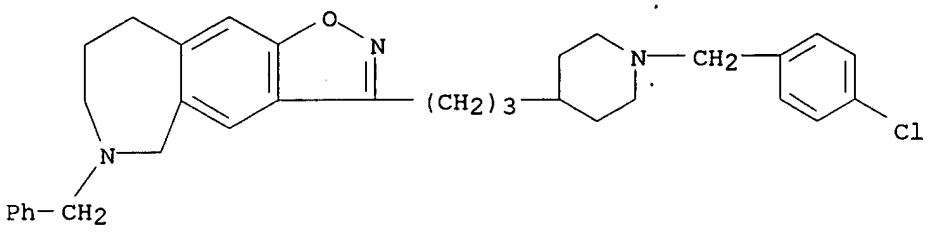


●2 HCl

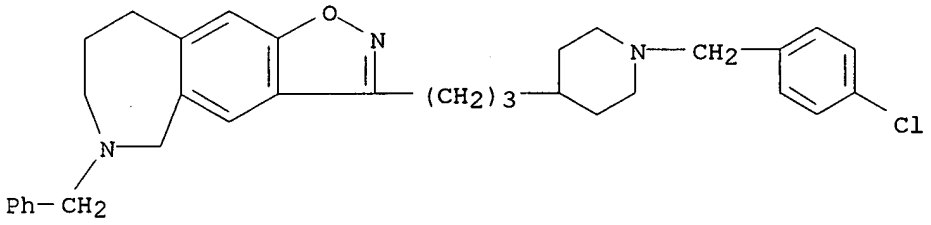
RN 265102-91-8 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 3-[3-[1-[(3-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-6-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 265102-92-9 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 3-[3-[1-[(4-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-6-(phenylmethyl)- (9CI) (CA INDEX NAME)

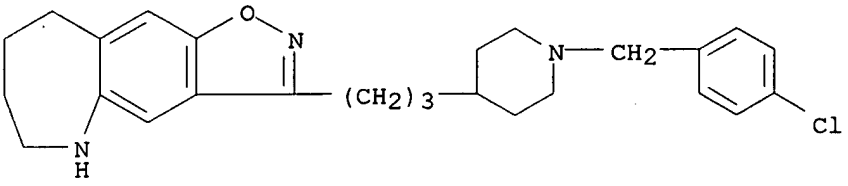


RN 265102-93-0 CAPLUS
CN 5H-Isoxazolo[5,4-h][2]benzazepine, 3-[3-[1-[(4-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-6-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)



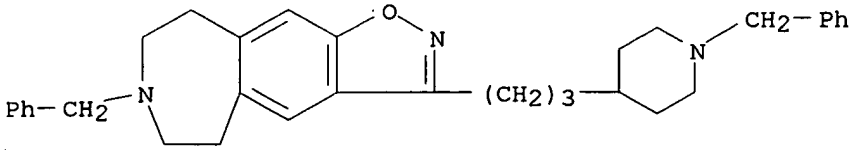
●2 HCl

RN 265102-94-1 CAPLUS
CN 5H-Isoxazolo[5,4-h][1]benzazepine, 3-[3-[1-[(4-chlorophenyl)methyl]-4-piperidinyl]propyl]-6,7,8,9-tetrahydro-, dihydrochloride (9CI) (CA INDEX NAME)



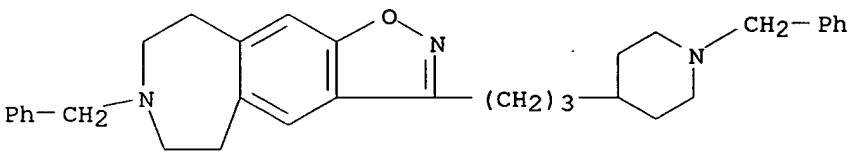
●2 HCl

RN 265103-15-9 CAPLUS
CN 5H-Isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-7-(phenylmethyl)-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



Searched by Barb O'Bryen, STIC 308-4291

RN 265103-16-0 CAPLUS
CN 5H-Isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-7-(phenylmethyl)-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, dihydrochloride (9CI) (CA INDEX NAME)



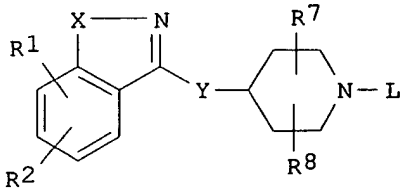
●2 HCl

REFERENCE COUNT: 78
REFERENCE(S): (1) Anon; CAPLUS
(2) Anon; CAPLUS
(3) Eisai Co Ltd; AU 9865209 A CAPLUS
(4) Eisai Co Ltd; WO 9843956 A1 1998 CAPLUS
(5) Eli Lilly And Company; JP 08188564 A CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L171 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:782696 CAPLUS
DOCUMENT NUMBER: 133:344629
TITLE: Treatment of age-related behavioral disorders of pets with acetylcholine esterase inhibitors, and pharmaceutical compositions containing piperidines for the treatment
INVENTOR(S): Landi, Christine Mary
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000309545	A2	20001107	JP 2000-114594	20000417
EP 1050303	A2	20001108	EP 2000-303253	20000413
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-131243 19990427
OTHER SOURCE(S): MARPAT 133:344629
GI



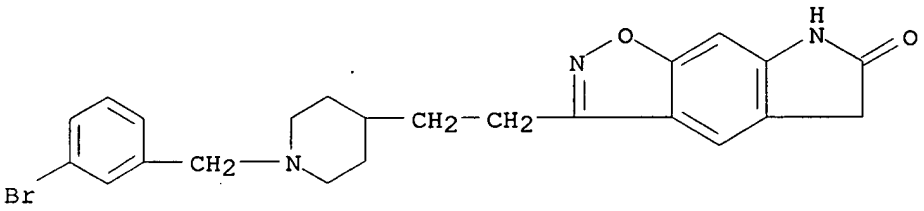
I

Searched by Barb O'Bryen, STIC 308-4291

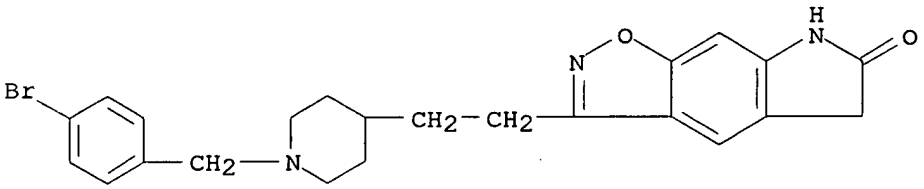
AB Age-related behavioral disorders (e.g. cognition disorder, amnesia, melancholia, and confusion) are treated by administration of an ED of piperidines I [R1, R2 = H, C1-6 alkoxy, (un)substituted PhCH2O, halo, NO2, amino, (un)substituted pyridylmethoxy, (un)substituted thienylmethoxy, etc.; X = O, S; Y = (CH2)m, CH:CH(CH2)n, O(CH2)m, etc.; m = 1-3; n = 0-3; L = (un)substituted Ph, cinnamyl, pyridylmethyl, etc.; R7, R8 = H, C1-6 alkyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, etc.], their salts, or their solvates as acetylcholine esterase inhibitors. Icopezil is effect for treatment of such disorders.

IT **145508-64-1 145508-65-2 145508-66-3 145508-68-5 145508-78-7 145508-87-8 145508-88-9**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of age-related behavioral disorders of pets with piperidines as acetylcholine esterase inhibitors)

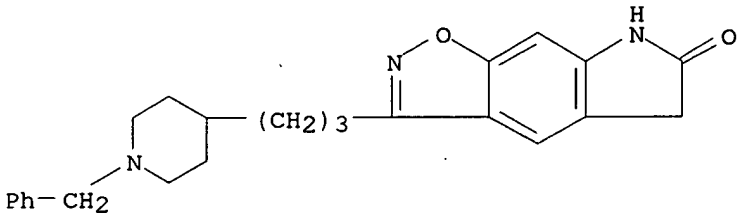
RN 145508-64-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(3-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)



RN 145508-65-2 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(4-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)

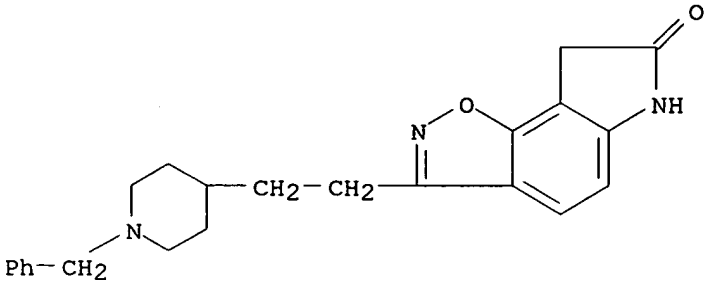


RN 145508-66-3 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)

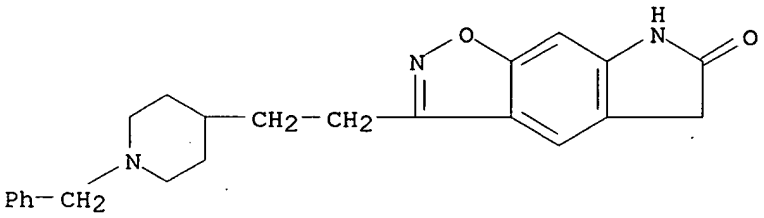


RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-

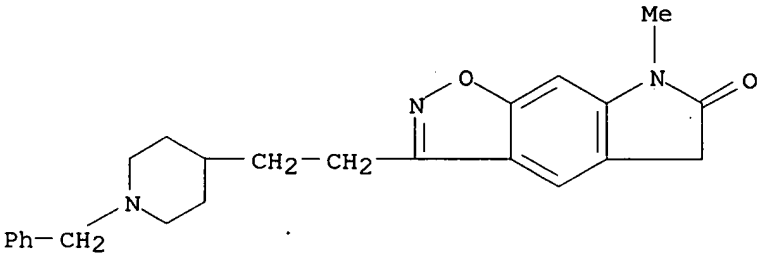
(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



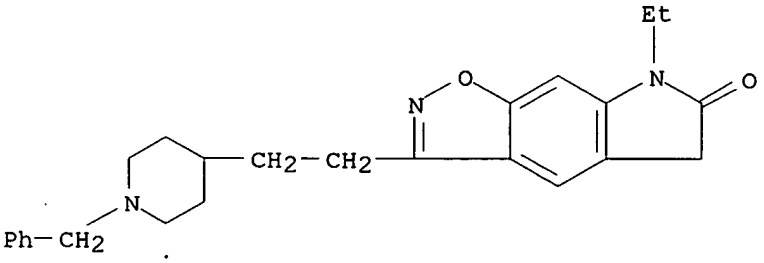
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-88-9 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

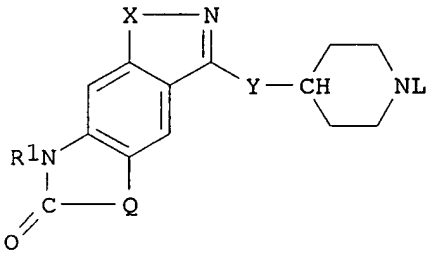


Searched by Barb O'Bryen, STIC 308-4291

L171 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:773886 CAPLUS
DOCUMENT NUMBER: 133:331554
TITLE: Radiotracers for in vivo study of acetylcholinesterase and Alzheimer's disease
INVENTOR(S): Bencherif, Badreddine; Frost, James J.; Dannals, Robert F.; Musachio, John; Scheffel, Ursula; Villalobos, Anabella
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1048302	A2	20001102	EP 2000-303348	20000420
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000351739	A2	20001219	JP 2000-125798	20000426

PRIORITY APPLN. INFO.: US 1999-132113 19990430
OTHER SOURCE(S): MARPAT 133:331554
GI



I

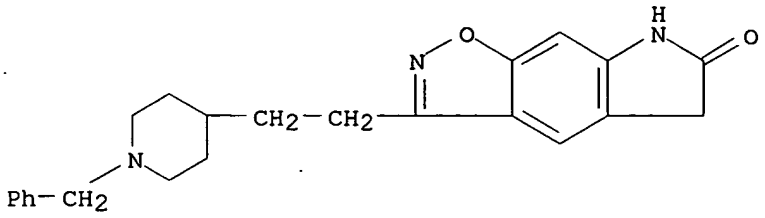
AB A preparative method for the 11C-labeled piperidinyl benzisoxazolone I is given. Such compds. are useful as in vivo imaging agents for diagnosis of Alzheimer's disease.

IT **145815-98-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 11C-labeled piperidinyl benzisoxazolone for brain acetylcholinesterase imaging)

RN 145815-98-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

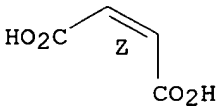
CRN 145508-78-7
CMF C23 H25 N3 O2



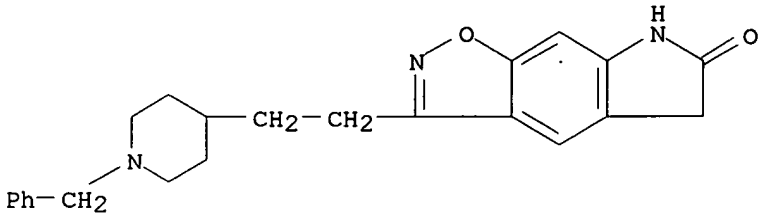
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

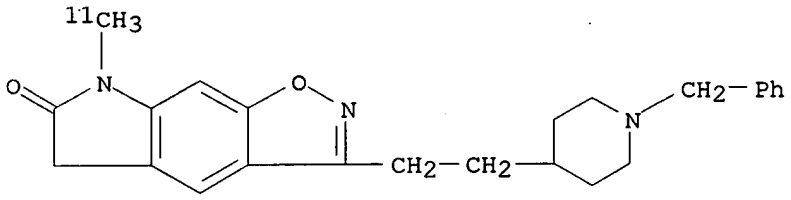
Double bond geometry as shown.



IT **145508-78-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 11C-labeled piperidinyl benzisoxazolone for brain acetylcholinesterase imaging)
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



IT **303728-79-2P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 11C-labeled piperidinyl benzisoxazolone for brain acetylcholinesterase imaging)
RN 303728-79-2 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-(methyl-11C)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

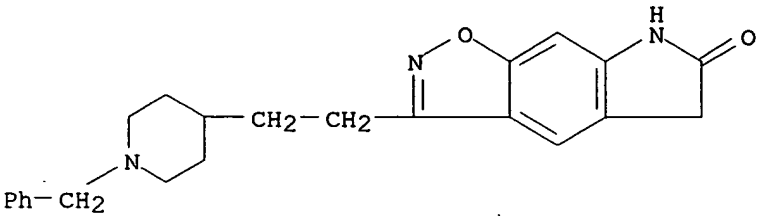


L171 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:84288 CAPLUS
DOCUMENT NUMBER: 132:132346
TITLE: A pharmaceutical composition for the prevention and treatment of diseases of cognitive dysfunction in a mammal
INVENTOR(S): Dasilva-Jardine, Paul A.
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 976404	A2	20000202	EP 1999-305938	19990726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9903240	A	20000509	BR 1999-3240	19990729
JP 2000143541	A2	20000523	JP 1999-214965	19990729
PRIORITY APPLN. INFO.:			US 1998-94653	19980730

AB Pharmaceutical compns. for the treatment of diseases involving cognitive dysfunction in a mammal comprising an estrogen agonist or antagonist or a pharmaceutically acceptable salt thereof; an acetyl cholinesterase inhibitor or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The estrogen agonists or antagonists and acetylcholinesterase inhibitors are present in amts. that render the compn. effective in the treatment of diseases of cognitive dysfunction including Alzheimer's Disease and Dementia. The compns. may help memory enhancement. An example estrogen agonist or antagonist is droloxifene and an example acetylcholinesterase inhibitor is donepezil.

IT **145508-78-7**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholinesterase inhibitor; pharmaceutical compn. for the prevention and treatment of diseases of cognitive dysfunction in a mammal)
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

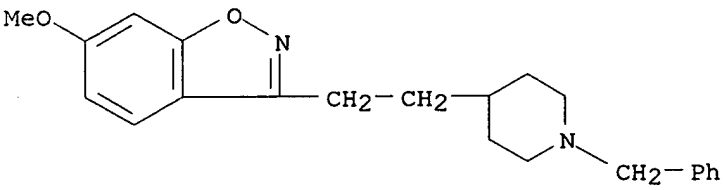


L171 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:184028 CAPLUS
DOCUMENT NUMBER: 132:329435
TITLE: Validation of protein-based alignment in 3D quantitative structure-activity relationships with CoMFA models
AUTHOR(S): Golbraikh, Alexander; Bernard, Philippe; Chretien, Jacques R.
CORPORATE SOURCE: Laboratory of Chemometrics and Bioinformatics, University of Orleans, Orleans, 45067, Fr.
SOURCE: Eur. J. Med. Chem. (2000), 35(1), 123-136
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

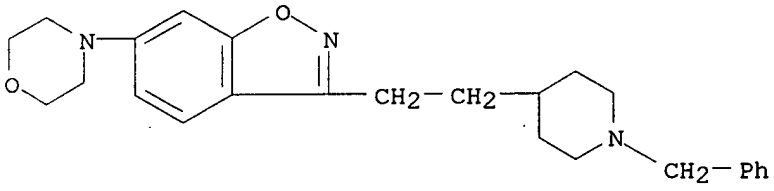
AB The predictive capabilities of protein-based alignment (PBA) and structure-based alignment (SBA) comparative mol. field anal. (CoMFA) models have been compared. 3D quant. structure-activity relationship (3D QSAR) models have been derived for a series of N-benzylpiperidine derivs. which are potent acetylcholinesterase (AChE) inhibitors interesting for Alzheimer's disease. To establish a comparison with the classical SBA procedure, different assay models were derived by superposing ligand conformers that are docked to the AChE active site and by using the most active compd. as the ref. one. A Kohonen self organizing map (SOM) was applied to analyze the mol. diversity of the test set relative to that of the training set, in order to explain the influence of mol. diversity on the predictive power of the considered models. SBA 3D QSAR models have to be used to predict the inhibitory activity only for compds. belonging to subgroups included in the training set. The PBA 3D QSAR models appeared to have a higher predictability, even for compds. with a mol. diversity greater than that of the training set. This results from the fact that the protein helps to automatically select the active conformation which is fitting the 3D QSAR model.

IT **145508-55-0 145508-56-1 145508-57-2**
145508-58-3 145508-59-4 145508-67-4
145508-68-5 145508-69-6 145508-70-9
145508-71-0 145508-72-1 145508-73-2
145508-74-3 145508-75-4 145508-76-5
145508-77-6 145508-78-7 145508-80-1
145508-82-3 145508-83-4 145508-84-5
145508-85-6 145508-87-8 145815-92-5
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(validation of protein-based alignment in 3D QSAR/CoMFA models of benzylpiperidine derivs. as acetylcholinesterase inhibitors)

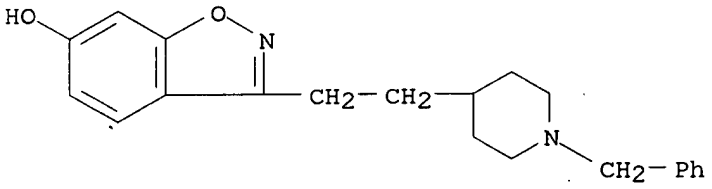
RN 145508-55-0 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



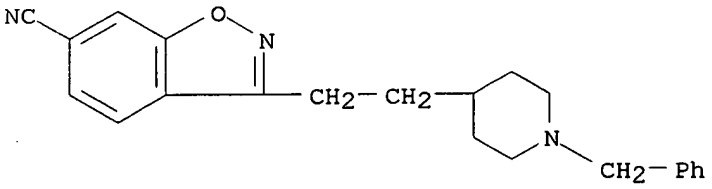
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



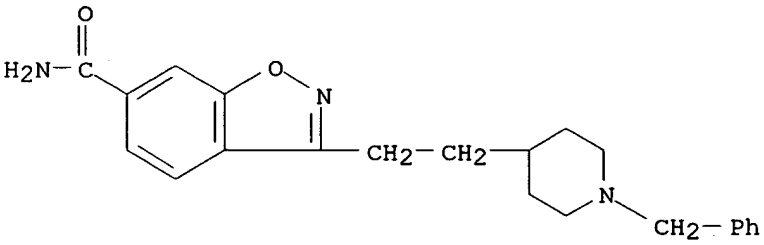
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



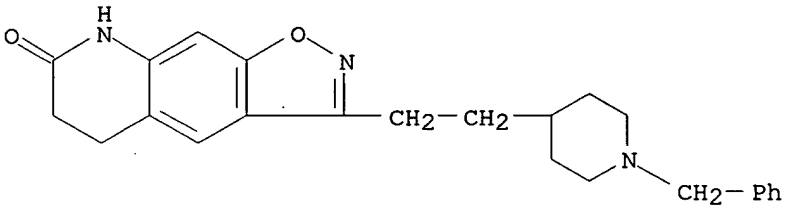
RN 145508-58-3 CAPLUS
CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



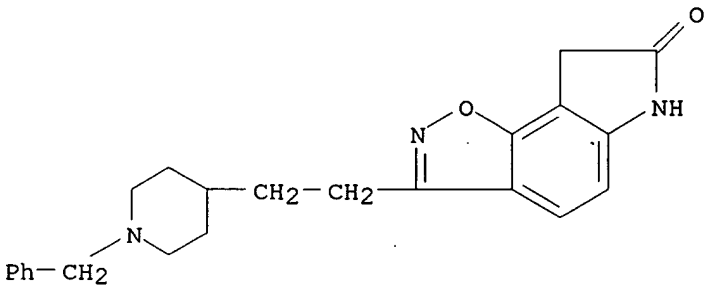
RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



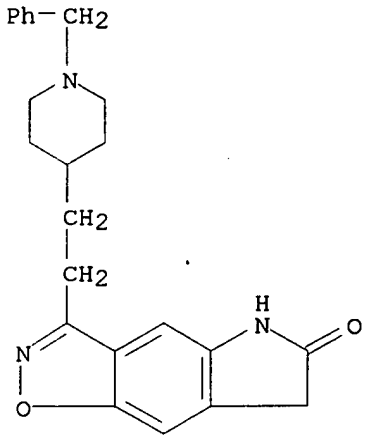
RN 145508-67-4 CAPLUS
CN Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



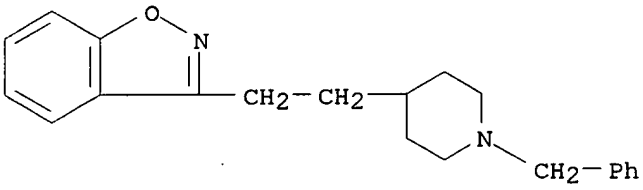
RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



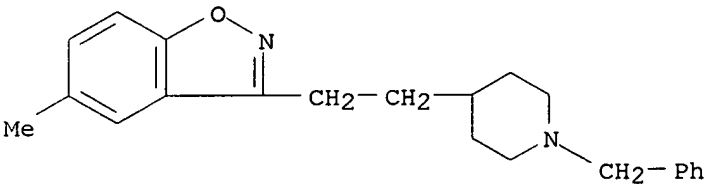
RN 145508-69-6 CAPLUS
CN 6H-Pyrrolo[2,3-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



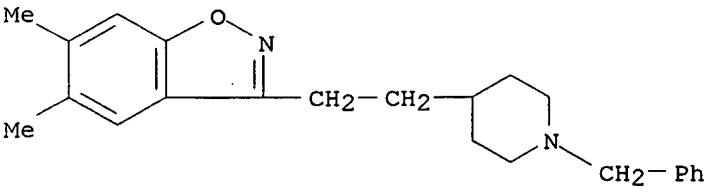
RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-71-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



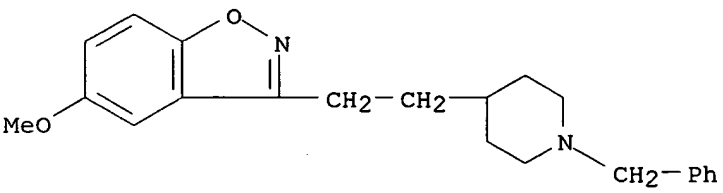
RN 145508-72-1 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



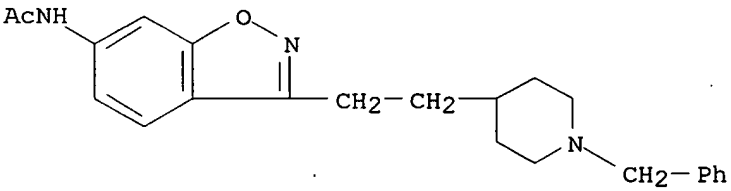
RN 145508-73-2 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

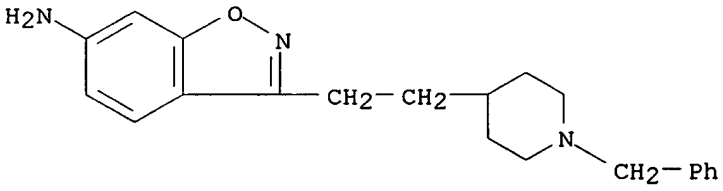
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



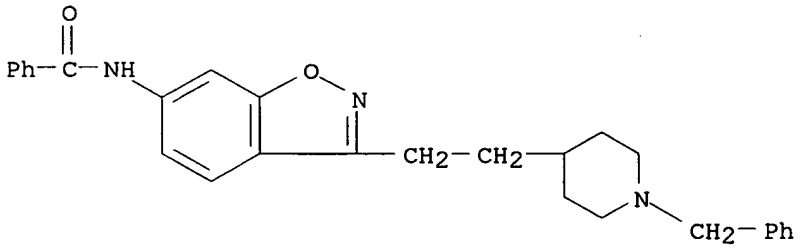
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



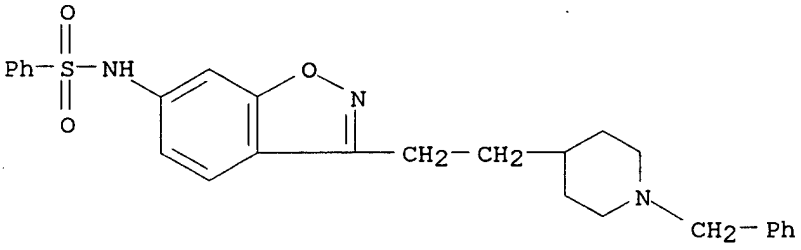
RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



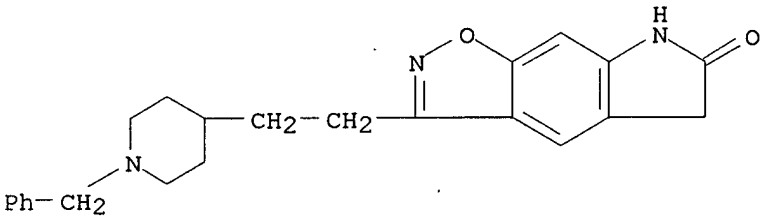
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



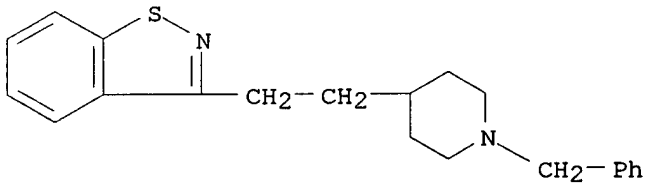
RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



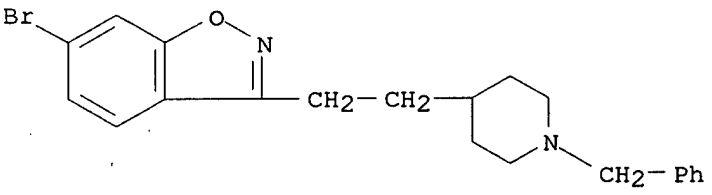
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



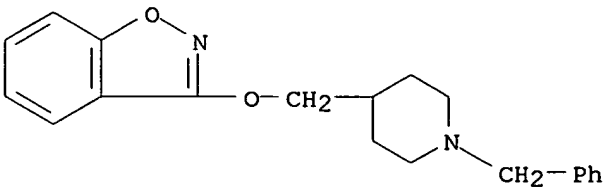
RN 145508-80-1 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



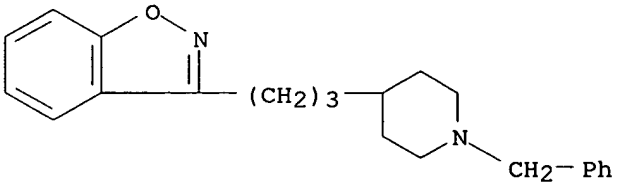
RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-83-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]- (9CI) (CA INDEX NAME)

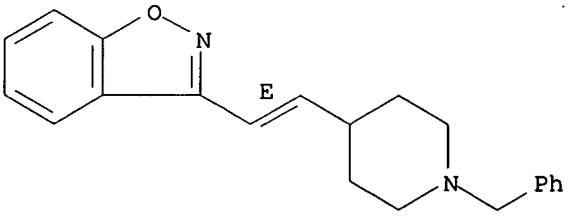


RN 145508-84-5 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)

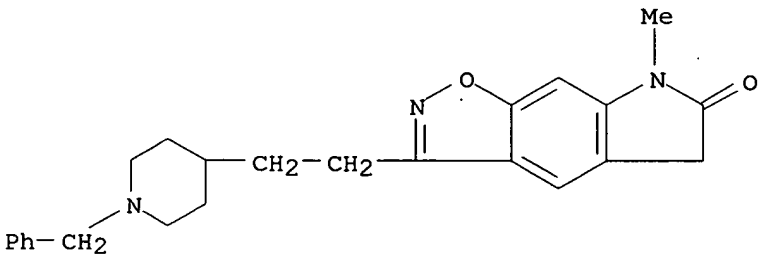


RN 145508-85-6 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-92-5 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

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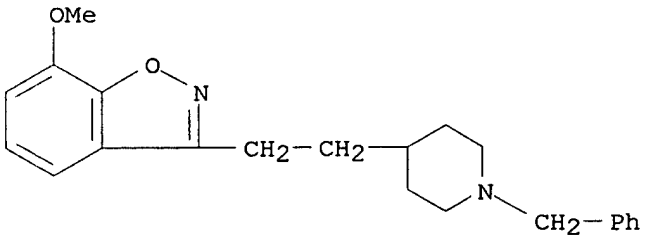


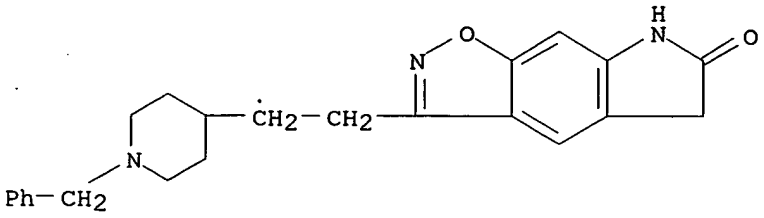
L171 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:613655 CAPLUS
DOCUMENT NUMBER: 131:248236
TITLE: Combination of a GABAA.alpha.5 inverse agonist and an acetylcholinesterase inhibitor for treatment of neurodegenerative diseases
INVENTOR(S): Dawson, Gerard Raphael
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947131	A2	19990923	WO 1999-GB778	19990316
WO 9947131	A3	19991104		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9928464	A1	19991011	AU 1999-28464	19990316
EP 1061952	A2	20001227	EP 1999-909095	19990316
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			GB 1998-5561	19980316
			WO 1999-GB778	19990316

AB The present invention relates to a combination of an acetylcholinesterase inhibitor and an inverse agonist of the GABAA.alpha.5 receptor subtype, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease.

IT **145508-78-7**, CP 118954
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(acetylcholinesterase inhibitor; combination of a GABAA.alpha.5 inverse agonist and an acetylcholinesterase inhibitor for treatment of neurodegenerative diseases)

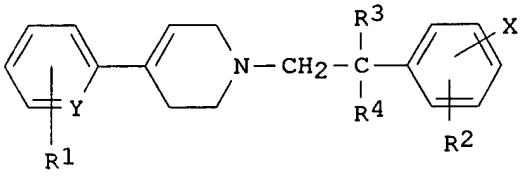
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



L171 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:344855 CAPLUS
DOCUMENT NUMBER: 131:715
TITLE: Combination of tetrahydropyridins and acetylcholinesterase inhibiting agents for treating senile dementia such as Alzheimer
INVENTOR(S): Maffrand, Jean-Pierre; Soubrie, Philippe; Terranova, Jean-paul
PATENT ASSIGNEE(S): Sanofi, Fr.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925363	A1	19990527	WO 1998-FR2384	19981109
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2771007	A1	19990521	FR 1997-14322	19971114
FR 2771007	B1	20001201		
FR 2771006	A1	19990521	FR 1997-14324	19971114
FR 2771006	B1	20001201		
ZA 9809955	A	19990506	ZA 1998-9955	19981030
AU 9911609	A1	19990607	AU 1999-11609	19981109
EP 1030671	A1	20000830	EP 1998-954538	19981109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9814035	A	20000926	BR 1998-14035	19981109
NO 2000002450	A	20000714	NO 2000-2450	20000511
PRIORITY APPLN. INFO.:			FR 1997-14322	19971114
			FR 1997-14324	19971114
			WO 1998-FR2384	19981109

GI



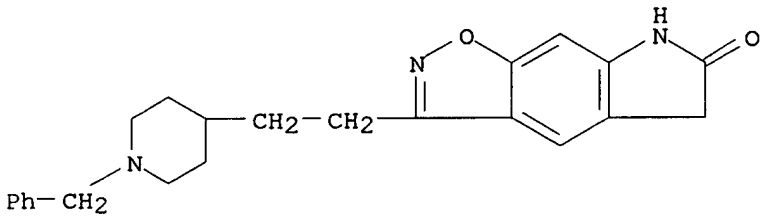
I

AB A pharmaceutical compn. contains as active principles: a constituent (a) selected between 1-(2-naphth-2-ylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin and a compd. (I) in which: Y represents -CH- or -N-; R1 represents hydrogen, a halogen, a hydroxyl, a CF3, a (C3-C4)alkyl group; R1 represents hydrogen, a halogen, a hydroxyl, a CF3, (C3-C4) alkyl group; R3 and R4 represent each hydrogen or a (C1-C4)alkyl; X represents (a) a (C3-C6)alkyl; a (C3-C6)alkoxyl; a (C3-C7)carboxyalkyl; (b) a radical selected among a (C3-C7)cycloalkyloxy, (C3-C7)cycloalkylmethyl, (C3-C7)cycloalkylamino and cyclohexenyl, said radical capable of being substituted by a halogen, hydroxy, (C1-C4)alkoxy, carboxy, (C1-C4)alkoxycarbonyl, amino, mono- or di-(C1-C4)alkylamino or (c) a group selected among Ph, phenoxy, phenylamino, N-(C1-C3)alkylphenylamino, phenylmethyl, phenylethyl, phenylcarbonyl, phenylthio, and styryl, said group capable of being mono- or polysubstituted on the Ph group by a halogen, CF3, (C1-C4)alkyl, (C1-C4)alkoxy, cyano, amino, mono- or di-(C1-C4)alkylamino; optionally in the form of one of its pharmaceutically acceptable salts. Also an constituent (b) active in the symptomatic treatment of DAT, optionally in the form of one of its pharmaceutically acceptable salts, provided that when constituent (a) is other than 1-(2-naphth-2-ylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin or one of its pharmaceutically acceptable salts, the constituent (b) is an acetylcholinesterase inhibiting agent. Combination of 5mg/kg oral SR 57746A and 1 mg/kg i.p. tacrine improved the memory of rats significantly.

IT **145508-78-7**, Icopezil
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of tetrahydropyridins and acetylcholinesterase inhibiting agents for treating senile dementia such as Alzheimer)

RN 145508-78-7 CAPLUS

CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5
REFERENCE(S):
(1) Interneuron Pharma; WO 9627380 A 1996 CAPLUS
(2) Kaminski Ram; US 5453428 A 1995 CAPLUS
(3) Porsolt; DRUG DEVELOPMENT RESEARCH 1995, V35(4), P214 CAPLUS
(4) Sanofi Sa; EP 0458696 A 1991 CAPLUS
(5) Sanofi Sa; WO 9701536 A 1997 CAPLUS

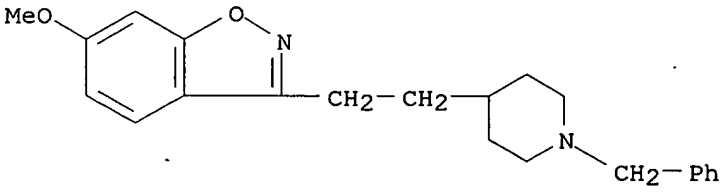
Searched by Barb O'Bryen, STIC 308-4291

L171 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:476811 CAPLUS
DOCUMENT NUMBER: 131:252093
TITLE: Automated docking of 82 N-benzylpiperidine derivatives to mouse acetylcholinesterase and comparative molecular field analysis with "natural" alignment
AUTHOR(S): Bernard, Philippe; Kireev, Dmitri B.; Chretien, Jacques R.; Fortier, Pierre-Louis; Coppet, Lucien
CORPORATE SOURCE: Laboratoire de Chimiometrie, Universite d'Orleans, Orleans, F-45067, Fr.
SOURCE: J. Comput.-Aided Mol. Des. (1999), 13(4), 355-371
CODEN: JCADEQ; ISSN: 0920-654X
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

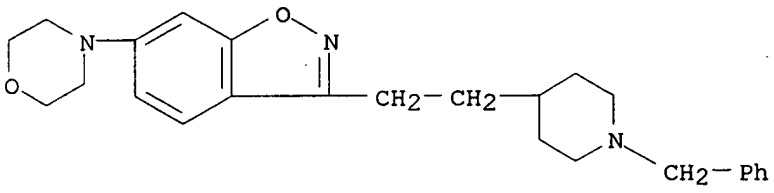
AB Automated docking and three-dimensional Quant. Structure-Activity Relationship studies (3D QSAR) were performed for a series of 82 reversible, competitive and selective acetylcholinesterase (AChE) inhibitors. The suggested automated docking technique, making use of constraints taken from exptl. crystallog. data, allowed to dock all the 82 substituted N-benzylpiperidines to the crystal structure of mouse AChE, because of short computational times. A 3D QSAR model was then established using the CoMFA method. In contrast to conventional CoMFA studies, the compds. were not fitted to a ref. mol. but taken in their "natural" alignment obtained by the docking study. The established and validated CoMFA model was then applied to another series of 29 N-benzylpiperidine derivs. whose AChE inhibitory activity data were measured under different exptl. conditions. A good correlation between predicted and exptl. activity data shows that the model can be extended to AChE inhibitory activity data measured on another acetylcholinesterase and/or at different incubation times and pH level.

IT **145508-55-0 145508-56-1 145508-57-2**
145508-58-3 145508-59-4 145508-67-4
145508-68-5 145508-69-6 145508-70-9
145508-71-0 145508-72-1 145508-73-2
145508-74-3 145508-75-4 145508-76-5
145508-77-6 145508-78-7 145508-80-1
145508-82-3 145508-83-4 145508-84-5
145508-85-6 145508-87-8 145815-92-5
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(automated docking of N-benzylpiperidine derivs. to mouse acetylcholinesterase and comparative mol. field anal. with natural alignment in relation to enzyme inhibitor activity)

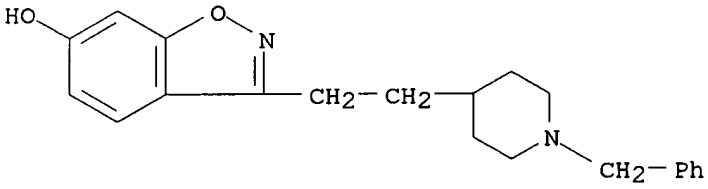
RN 145508-55-0 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



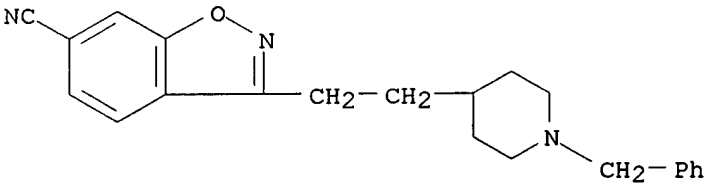
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



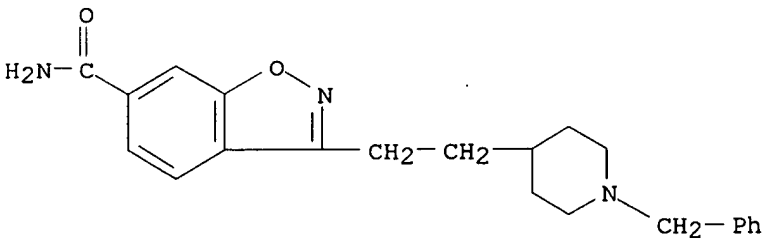
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



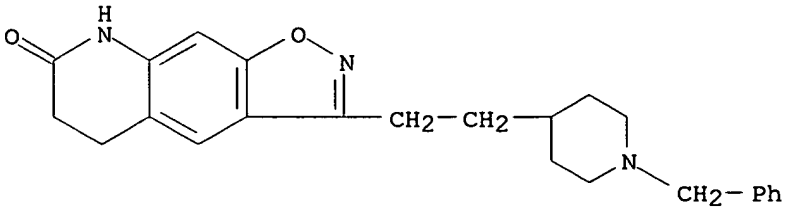
RN 145508-58-3 CAPLUS
CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



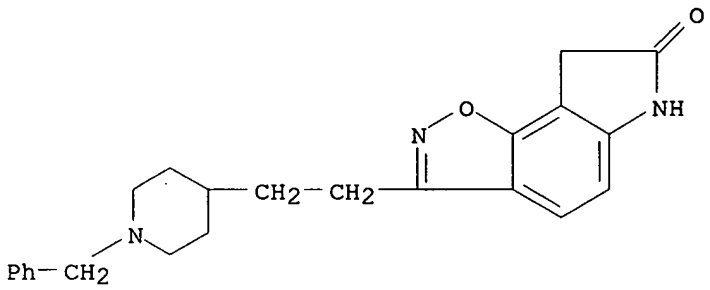
RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



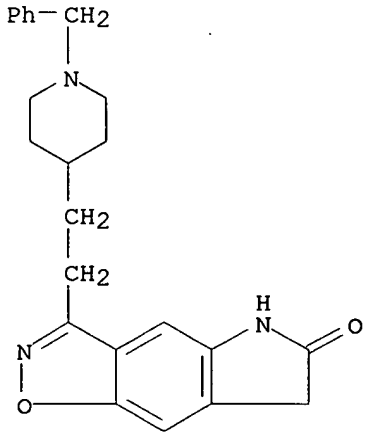
RN 145508-67-4 CAPLUS
CN Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



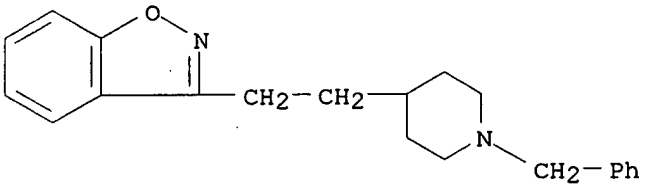
RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



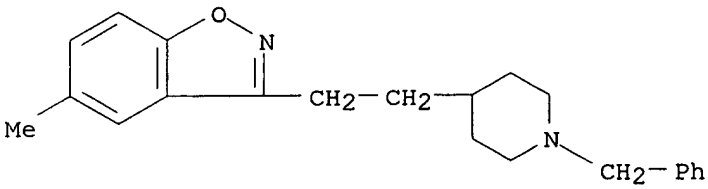
RN 145508-69-6 CAPLUS
CN 6H-Pyrrolo[2,3-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



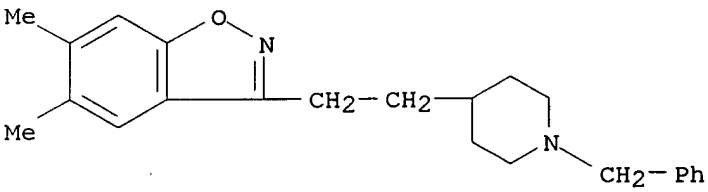
RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



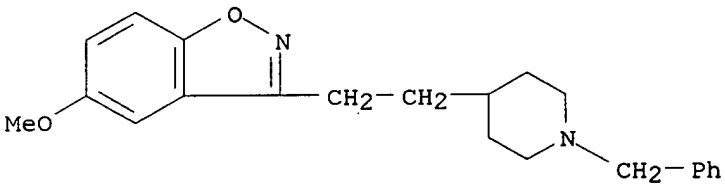
RN 145508-71-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



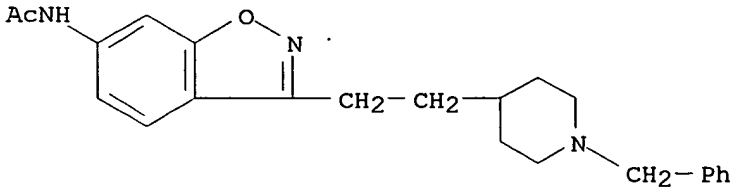
RN 145508-72-1 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



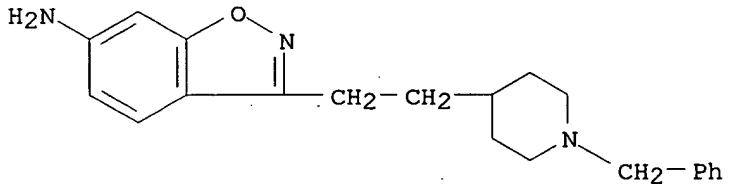
RN 145508-73-2 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



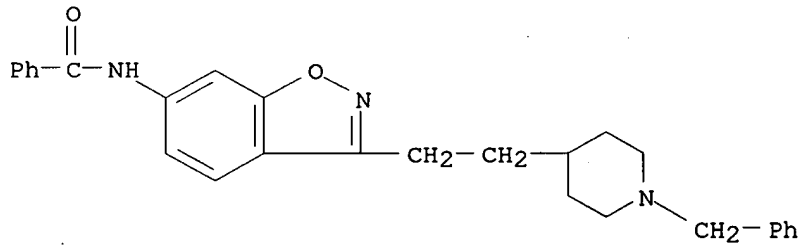
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



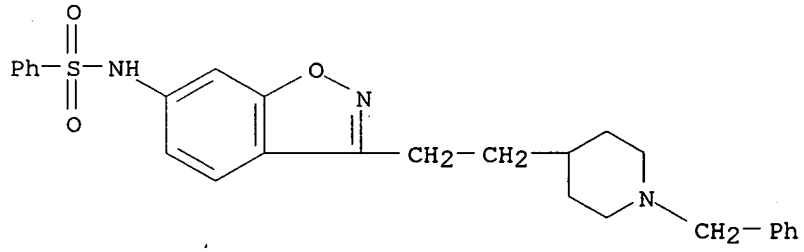
RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



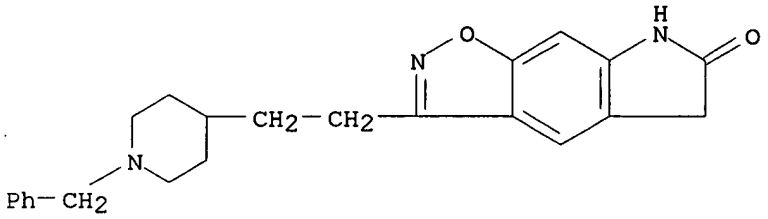
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



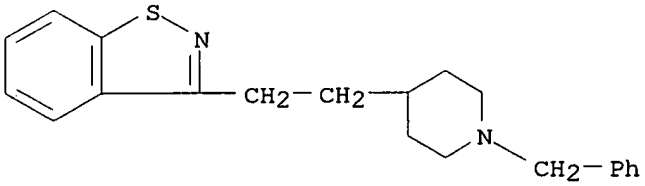
RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



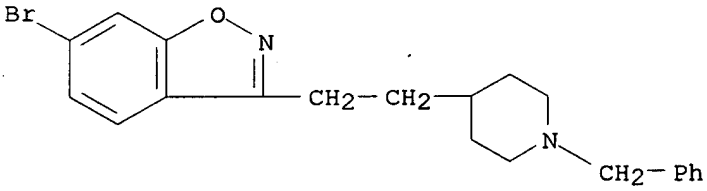
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



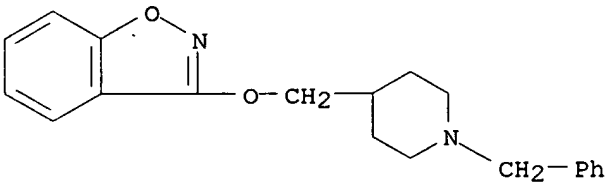
RN 145508-80-1 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



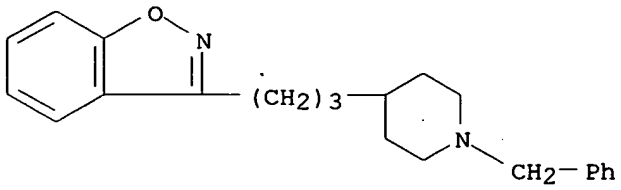
RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-83-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]- (9CI) (CA INDEX NAME)

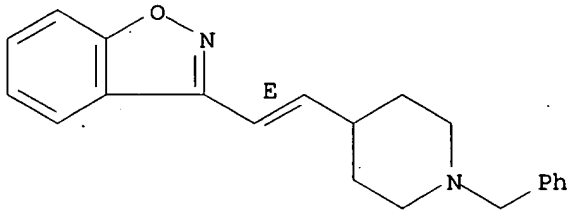


RN 145508-84-5 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)

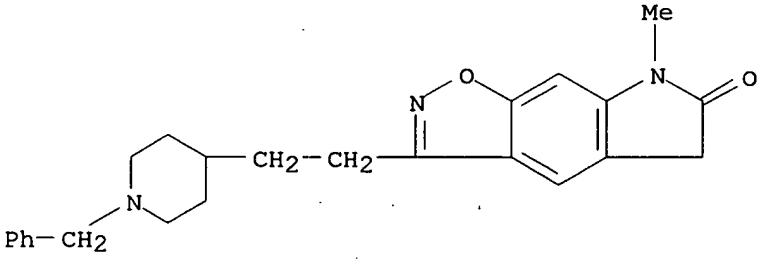


RN 145508-85-6 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]- (9CI) (CA INDEX NAME)

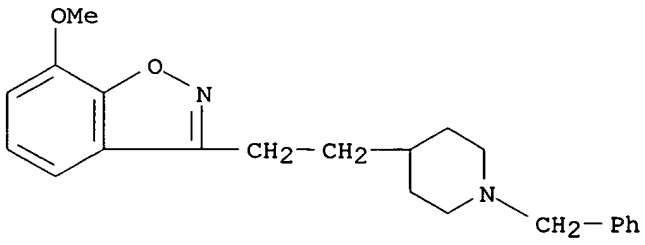
Double bond geometry as shown.



RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-92-5 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



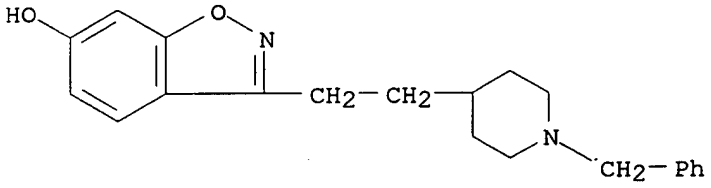
REFERENCE COUNT: 34
REFERENCE(S): (1) Barnard, E; The Peripheral Nervous System 1974, P201 CAPLUS
(2) Becker, R; Drug Dev Res 1988, V12, P163 CAPLUS
Searched by Barb O'Bryen, STIC 308-4291

(4) Cardozo, M; J Med Chem 1992, V35, P584 CAPLUS
(5) Cho, S; J Med Chem 1996, V39, P5064 CAPLUS
(8) Cramer, R; J Am Chem Soc 1988, V110, P5959 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L171 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:39701 CAPLUS
DOCUMENT NUMBER: 130:264102
TITLE: Synthesis and evaluation of 6-[11C]methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1, 2-benzisoxazole as an in vivo radioligand for acetylcholinesterase
AUTHOR(S): Brown-Proctor, Clive; Snyder, Scott E.; Sherman, Phillip S.; Kilbourn, Michael R.
CORPORATE SOURCE: Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, 48109-0552, USA
SOURCE: Nucl. Med. Biol. (1998), Volume Date 1999, 26(1), 99-103
CODEN: NMBIEO; ISSN: 0969-8051
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

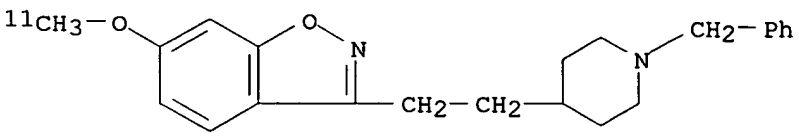
AB 6-Methoxy-3-[2-[1-(phenylmethyl) -4-piperidinyl]ethyl]-1,2-benzisoxazole is a high affinity (Ki = 8.2 nM) reversible inhibitor of acetylcholinesterase (AChE). The carbon-11 labeled form was prepd. in high (>97%) radiochem. purity and with specific activities of 37 .+-. 20 GBq/.mu.mol at end of synthesis, by the alkylation of the desmethyl precursor with [11C]methyl trifluoromethanesulfonate in N,N-dimethylformamide at room temp. In vivo studies in mice demonstrated good blood brain permeability but essentially uniform regional brain distribution. Thus, despite in vitro and in vivo activity as an AChE inhibitor, 6-[11C]methoxy-3-[2-[1-(phenylmethyl) -4-piperidinyl]ethyl]-1,2-benzisoxazole does not appear to be a good candidate for in vivo imaging studies of AChE in the mammalian brain.

IT **145508-57-2**
RL: RCT (Reactant)
(reactant; synthesis and evaluation of reactant 6-[11C]methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole as an in vivo radioligand for acetylcholinesterase)
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



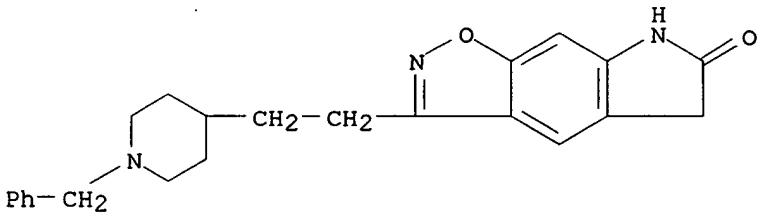
IT **222051-31-2P**
RL: BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(synthesis and evaluation of reactant 6-[11C]methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole as an in vivo radioligand for acetylcholinesterase)
RN 222051-31-2 CAPLUS
CN 1,2-Benzisoxazole, 6-(methoxy-11C)-3-[2-[1-(phenylmethyl)-4-

piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30
REFERENCE(S):
(2) Davies, P; Brain Res 1979, V171, P319 CAPLUS
(3) Dischino, D; J Nucl Med 1983, V24, P1030 CAPLUS
(6) Geula, C; Alzheimer Disease 1994, P263 CAPLUS
(7) Giacobini, E; Alzheimer Disease:Therapeutic Strategies 1994, P155 CAPLUS
(9) Gordon, M; Brain Res 1984, V308, P364 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

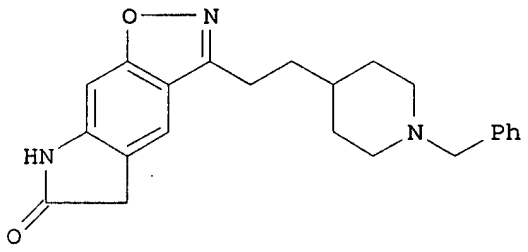
L171 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:539712 CAPLUS
DOCUMENT NUMBER: 127:225205
TITLE: Effect of drug particle size on content uniformity of low-dose solid dosage forms
AUTHOR(S): Zhang, Ying; Johnson, Kevin C.
CORPORATE SOURCE: Department of Pharmaceutical Research and Development, Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: Int. J. Pharm. (1997), 154(2), 179-183
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two low-dose blends were prepd. that differed only in the particle size of the drug used to make the blends. The geometric mean particle diams. for the two lots of drug used were 18.5 and 6.1 .mu.m. Samples of the blends approx. equiv. to the unit dose of 10 .mu.g per 99 mg of blend were assayed for potency. For the blend contg. the larger particle size drug, the potency range was 88-130% (n = 65) compared to 97-102% (n = 64) for the blend contg. the smaller particle size drug. A simple computer method was able to qual. simulate the obsd. potency profiles using only the particle size distribution of the drug and assuming ideal mixing. The method provides guidance in setting particle size specifications to avoid poor content uniformity.
IT **145508-78-7**, CP 118954
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of drug particle size on content uniformity of low-dose solid dosage forms)
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



L171 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:469505 CAPLUS
DOCUMENT NUMBER: 125:114591
TITLE: Processes and intermediates for preparing 5,7-dihydro-3-[2-(1-benzylpiperidin-4-yl)ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one
INVENTOR(S): Devries, Keith M.; Villalobos, Anabella
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9613505	A1	19960509	WO 1995-IB755	19950913
W: CA, FI, JP, MX, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2200607	AA	19960509	CA 1995-2200607	19950913
EP 788500	A1	19970813	EP 1995-929199	19950913
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 3048643	B2	20000605	JP 1995-514409	19950913
JP 3048643	B2	20000605	JP 1996-514409	19950913
JP 10502939	T2	19980317		
US 5916902	A	19990629	US 1997-836114	19970416
FI 9701785	A	19970425	FI 1997-1785	19970425
PRIORITY APPLN. INFO.:			US 1994-329352	19941026
			WO 1995-IB755	19950913

OTHER SOURCE(S): CASREACT 125:114591; MARPAT 125:114591
GI



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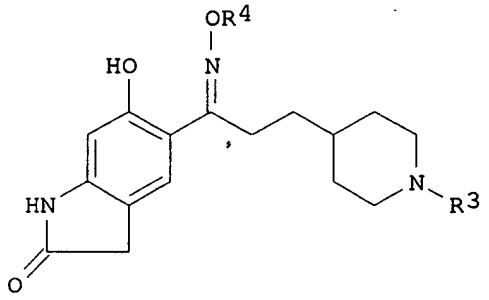


II

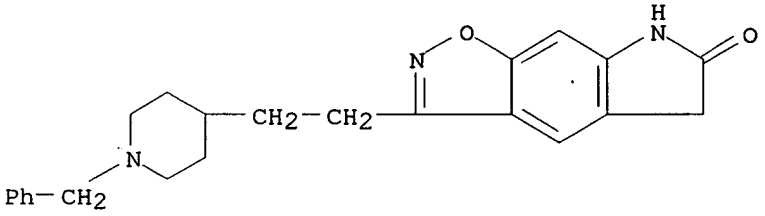
Searched by Barb O'Bryen, STIC 308-4291

AB The invention relates to a process for prepg. title compd. I, a known cholinesterase inhibitor useful for enhancing memory in patients suffering from dementia or Alzheimer's disease (no data). The method involves heating an oxime deriv. II [R3 = R4 or CH2Ph; R4 = R5CO, R5OCO, R5SO2; R5 = C1-6 alkyl or C6-10/C1-6 arylalkyl] at an elevated temp. in the presence of a base. In the case where R3 = R4, the product is further hydrolyzed with an aq. mineral acid at an elevated temp., followed by benzylation, either with a benzylating agent in the presence of a base, or with benzaldehyde in the presence of a reducing agent and an acid. For instance, pyridine-4-carboxaldehyde was converted in 6 steps to the oxime II [R3 = CO2Me, R4 = H]. Treatment of this with Ac2O and AcONa in THF at room temp. gave 92% II [R3 = CO2Me, R4 = Ac]. The latter was cyclized by 2,6-lutidine in THF at 65.degree. (72%), followed by hydrolysis of the ester with 6N HCl at 100.degree. (78%), and N-benzylation with either PhCH2Br and N(CH2CH2OH)3 (74%), or PhCHO, NaBH(OAc)3, and AcOH, to give I.

IT **145508-78-7P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of a dihydro[(benzylpiperidinyl)ethyl]pyrrolobenzisoxazolone)

RN 145508-78-7 CAPLUS

CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



L171 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:6908 CAPLUS

DOCUMENT NUMBER: 124:105610

TITLE: A Comparative Molecular Field Analysis Study of N-Benzylpiperidines as Acetylcholinesterase Inhibitors

AUTHOR(S): [redacted] Tong, Weida; Collantes, Elizabeth R.; Chen, Yu; Welsh, William J.

CORPORATE SOURCE: Department of Chemistry, University of Missouri, St. Louis, MO, 63121, USA

SOURCE: [redacted] J. Med. Chem. (1996), 39(2), 380-7
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

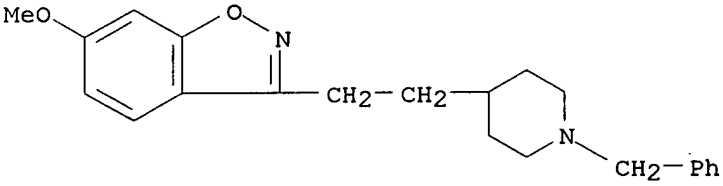
LANGUAGE: English

AB A series of 1-benzyl-4-[2-(N-benzoylamino)ethyl]piperidine derivs. and of N-benzylpiperidine benzisoxazoles have been investigated using the comparative mol. field anal. (CoMFA) approach. These compds. have been found to inhibit the metabolic breakdown of the neurotransmitter acetylcholine (ACh) by the enzyme acetylcholinesterase (AChE) and hence alleviate memory deficits in patients with Alzheimer's disease by potentiating cholinergic transmission. Development of the CoMFA model considered two sep. alignments: (i) alignment I which emphasized the electrostatic fitting of the subject compds. and (ii) alignment II which emphasized their steric fitting. In addn., the inhibitor compds. were considered both as neutral species and as N-piperidine-protonated species. The resulting 3D-QSAR indicates a strong correlation between the inhibitory activity of these N-benzylpiperidines and the steric and electronic factors which modulate their biochem. activity. A CoMFA model

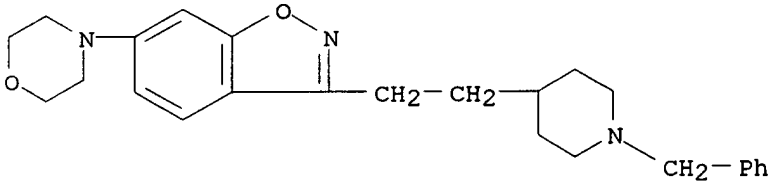
with considerable predictive ability was obtained.

IT **145508-55-0 145508-56-1 145508-57-2**
145508-58-3 145508-59-4 145508-70-9
145508-71-0 145508-72-1 145508-73-2
145508-74-3 145508-75-4 145508-76-5
145508-77-6 145508-80-1 145508-82-3
145508-83-4 145508-84-5 145815-92-5
172956-52-4
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative mol. field anal. study of N-benzylpiperidines as acetylcholinesterase inhibitors)

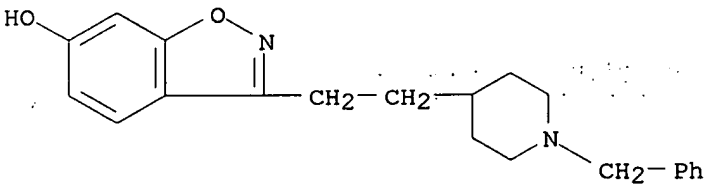
RN 145508-55-0 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



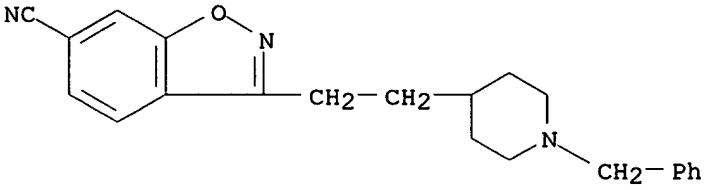
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



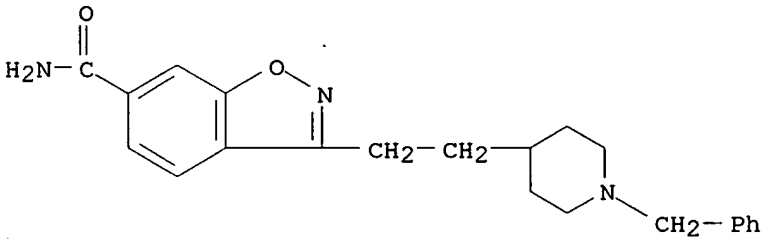
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



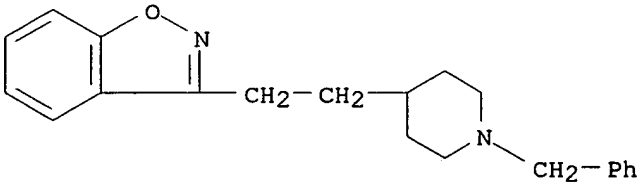
RN 145508-58-3 CAPLUS
CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



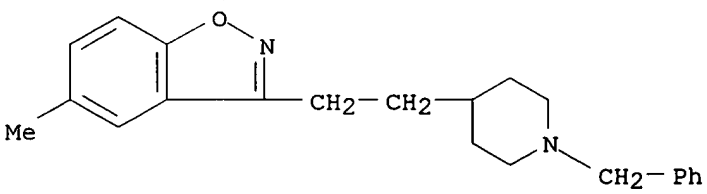
RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



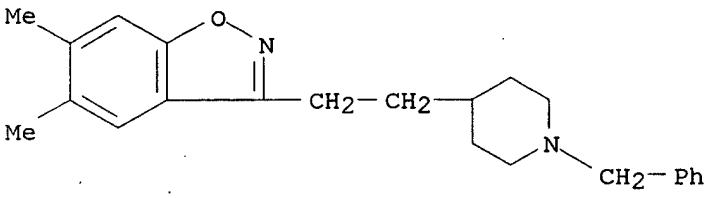
RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



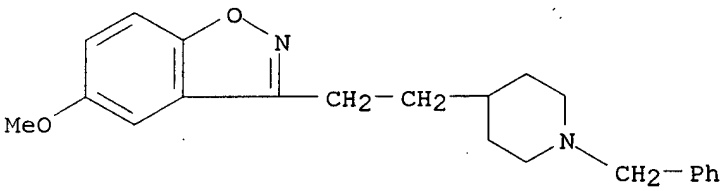
RN 145508-71-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



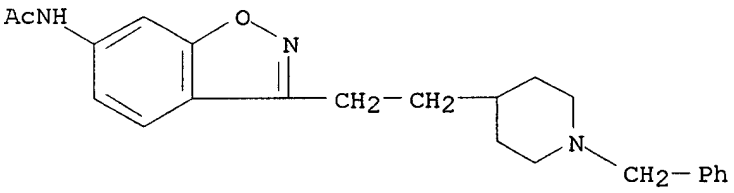
RN 145508-72-1 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



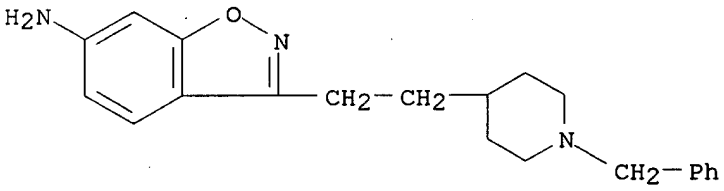
RN 145508-73-2 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



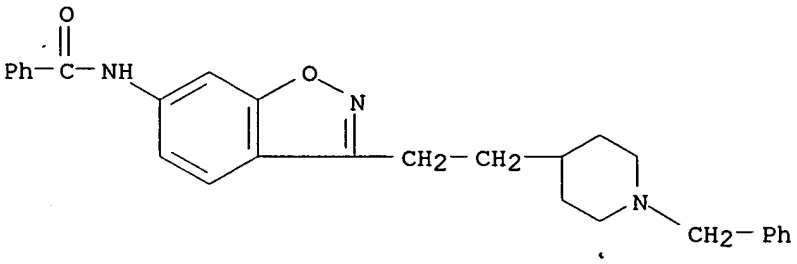
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



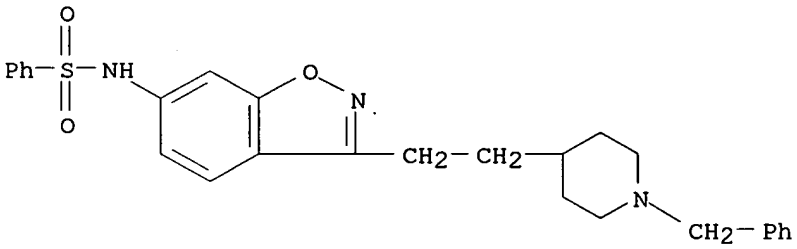
RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



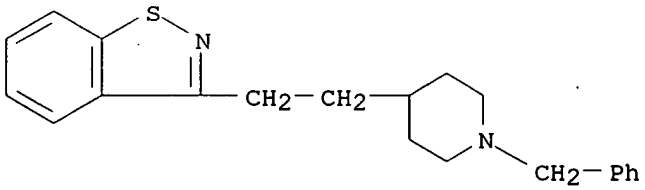
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



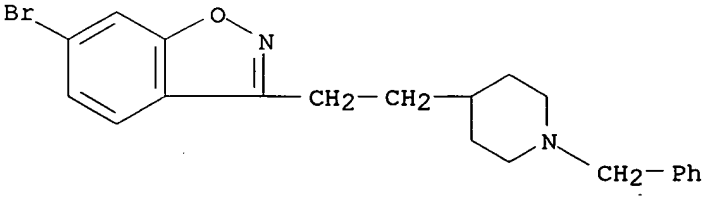
RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



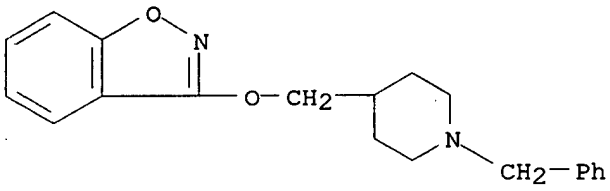
RN 145508-80-1 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



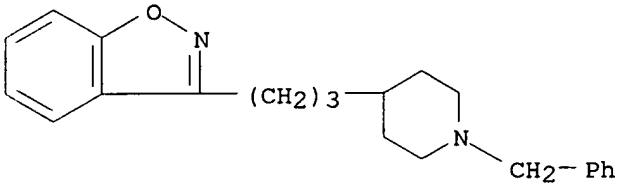
RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



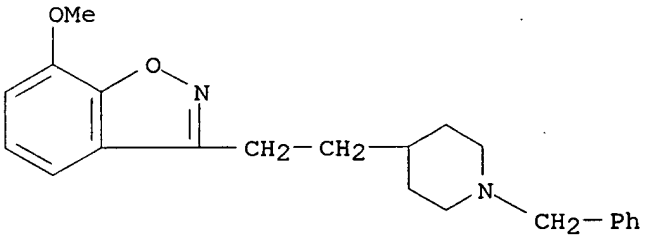
RN 145508-83-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]- (9CI) (CA INDEX NAME)



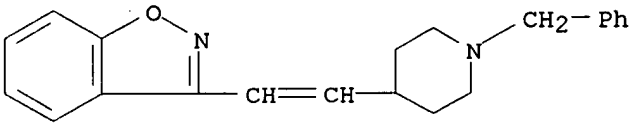
RN 145508-84-5 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



RN 145815-92-5 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 172956-52-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]- (9CI) (CA INDEX NAME)



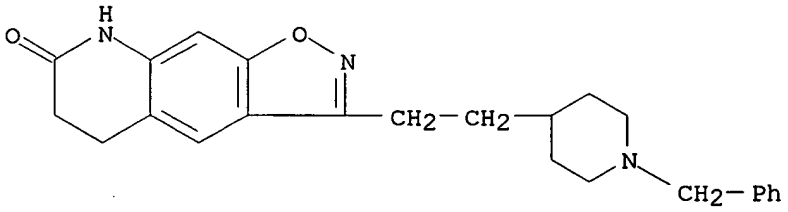
L171 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:665454 CAPLUS
DOCUMENT NUMBER: 123:143809
TITLE: 5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[3,2-f]-1,2-benzisoxazol-6-one: A Potent and Centrally-Selective Inhibitor of Acetylcholinesterase
AUTHOR(S): Villalobos, Anabella; Butler, Todd W.; Chapin, Douglas
Searched by Barb O'Bryen, STIC 308-4291

S.; Chen, Yuhpyng L.; DeMattos, Steven B.; Ives, Jeffrey L.; Jones, Shawn B.; Liston, Dane R.; Nagel, Arthur A.; et al.
CORPORATE SOURCE: Central Research Division, Pfizer Inc., Groton, CT, 06340, USA
SOURCE: J. Med. Chem. (1995), 38(15), 2802-8
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

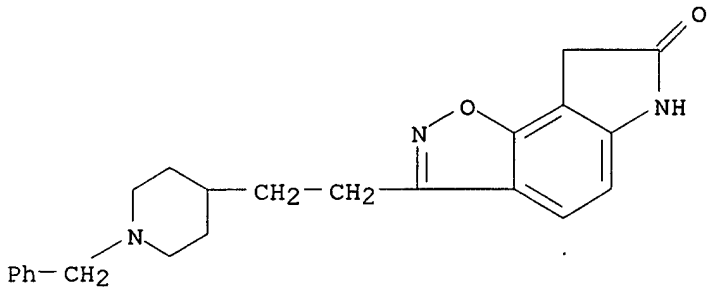
AB A series of N-benzylpiperidines with novel isoxazole-contg. tricycles has been prepd. This series has shown potent in vitro inhibition of the enzyme acetylcholinesterase (AChE), with IC50s = 0.33-3.6 nM. The title compds. displayed weak in vitro inhibition of butyrylcholinesterase (BuChE) with IC50s = 600-23 000 nM. 5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[3,2-f]-1,2-benzisoxazol-6-one (I) also displayed a favorable profile in vivo. In microdialysis expts., I produced a 200% increase in extracellular levels of acetylcholine (ACh) at a dose of 0.4 mg/kg in freely moving, conscious rats. Peripheral side effects (salivation ED50 = 26 .+-. 1.5 mg/kg) and acute lethality (LD50[1 h] = 42 mg/kg) were obsd. at >60-fold higher doses. Compd. I , designated as CP-118,954, is currently in clin. development for the treatment of cognitive disorders.

IT **145508-67-4P**, Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]
145508-68-5P, 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]
145508-78-7P, 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-
145508-87-8P, 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]
145815-98-1P, 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl], (Z)-2-butenedioate (1:1) **145816-07-5P**, 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl], monomethanesulfonate
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
((piperidinylethyl)pyrrolo[3,2-f]-1,2-benzisoxazolones acetylcholinesterase inhibitors)

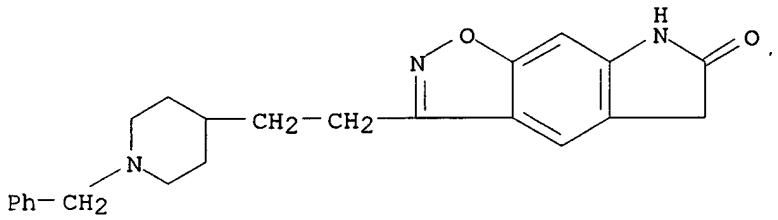
RN 145508-67-4 CAPLUS
CN Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



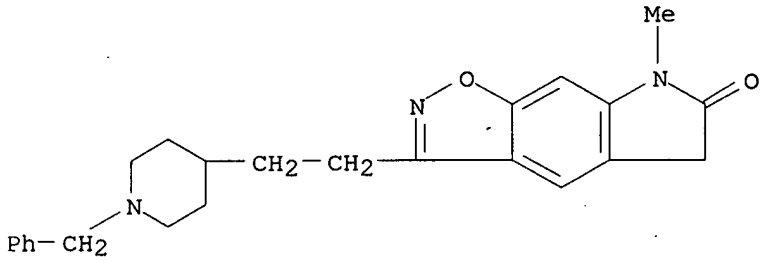
RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



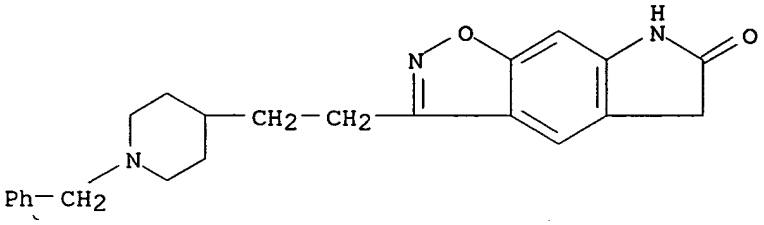
RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-98-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

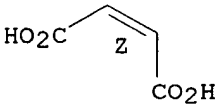
CRN 145508-78-7
CMF C23 H25 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

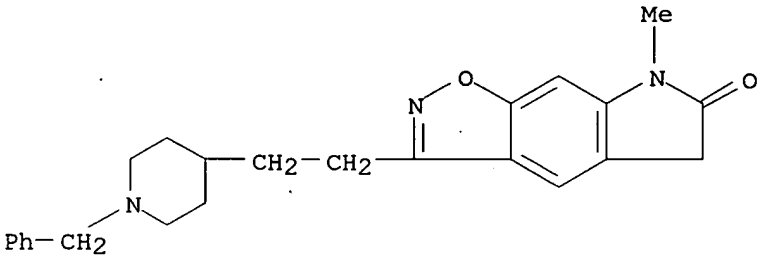
Double bond geometry as shown.



RN 145816-07-5 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

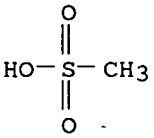
CM 1

CRN 145508-87-8
CMF C24 H27 N3 O2

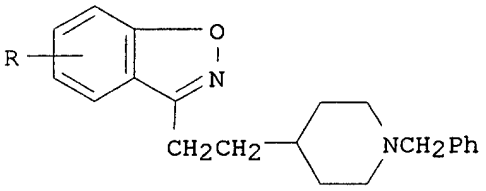


CM 2

CRN 75-75-2
CMF C H4 O3 S



L171 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:579520 CAPLUS
DOCUMENT NUMBER: 121:179520
TITLE: Novel Benzisoxazole Derivatives as Potent and Selective Inhibitors of Acetylcholinesterase
AUTHOR(S): Villalobos, Anabella; Blake, James F.; Biggers, C. Kelly; Butler, Todd W.; Chapin, Douglas S.; Chen, Yuhpyng L.; Ives, Jeffrey L.; Jones, Shawn B.; Liston, Dane R.; et al.
CORPORATE SOURCE: Department of Medicinal Chemistry, Pfizer Inc., Groton, CT, 06340, USA
SOURCE: J. Med. Chem. (1994), 37(17), 2721-34
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



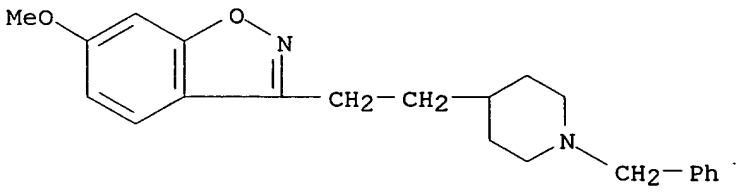
I

AB A series of N-benzylpiperidine benzisoxazoles I [R = H, 5-Me, 5,6-Me2, 5-OMe, 6-OMe, 7-OMe, 6-NHAc, 6-NHSO2Ph, 6-morpholino, 6-NH2, 6-OH, 6-Br, 6-CN, 6-CONH2] and some related compds. has been developed as potent and selective inhibitors of the enzyme acetylcholinesterase (AChE). The benzisoxazole heterocycle was found to be an appropriate bioisosteric replacement for the benzoyl functionality present in the N-benzylpiperidine class of inhibitors. The title compds. were synthesized by alkylating 3-methyl-1,2-benzisoxazoles with an iodo piperidine deriv. as the key step. I displayed potent inhibition of AChE in vitro with IC50's = 0.8-14 nM. Particularly interesting were I [R = 6-NHAc, morpholino]with IC50 = 3 nM and 0.8 nM, resp., which displayed outstanding selectivity for acetyl- over butyrylcholinesterase, in excess of 3 orders of magnitude. I [R = NHAc] also displayed a favorable profile in vivo. This analog showed a dose-dependent elevation of total acetylcholine in mouse forebrain after oral administration with an ED50 = 2.4 mg/kg. In addn., I [R = NHAc] was able to reverse amnesia in a mouse passive avoidance model at doses of 3.2 and 5.6 mg/kg with an av. reversal of 89.7%. Mol. dynamics simulations were used to study the possible binding modes of I to AChE from Torpedo californica. Key structural insights were obtained regarding the potency of this class of inhibitors. Specifically, Asp-72, Trp-84, Trp-279, Phe-288, and Phe-330 are implicated in the binding of these inhibitors. I may be suitable compds. for the palliative treatment of Alzheimer's Disease.

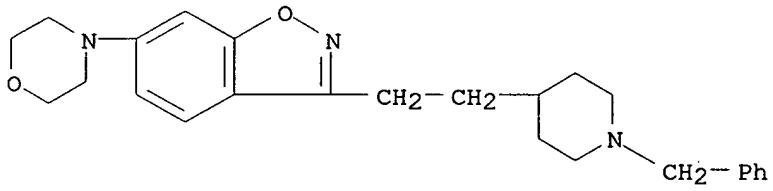
IT **145508-55-0P 145508-56-1P 145508-57-2P**
145508-58-3P 145508-59-4P 145508-70-9P
145508-71-0P 145508-72-1P 145508-73-2P
145508-74-3P 145508-75-4P 145508-76-5P
145508-77-6P 145508-80-1P 145508-82-3P
145508-83-4P 145508-84-5P 145508-85-6P
145815-88-9P 145815-89-0P 145815-90-3P
145815-91-4P 145815-92-5P 145815-93-6P
145815-94-7P 145815-95-8P 145815-96-9P
145815-97-0P 145816-00-8P 145816-03-1P

145816-04-2P 145816-05-3P 157640-16-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and acetylcholinesterase-inhibiting activity of)

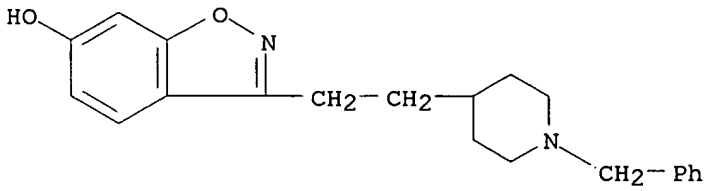
RN 145508-55-0 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



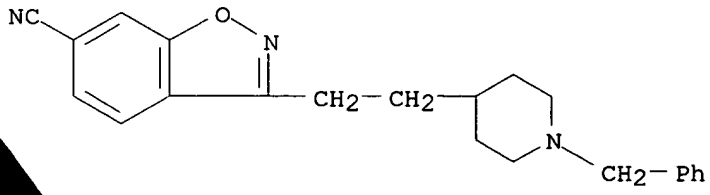
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

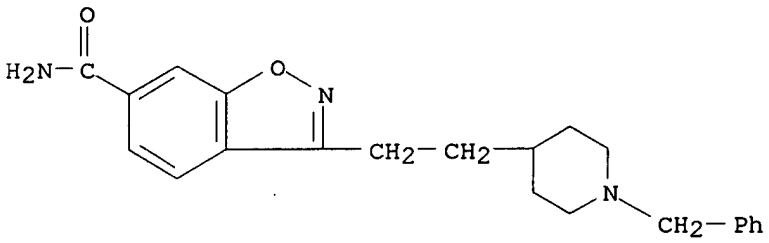


RN 145508-58-3 CAPLUS
CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

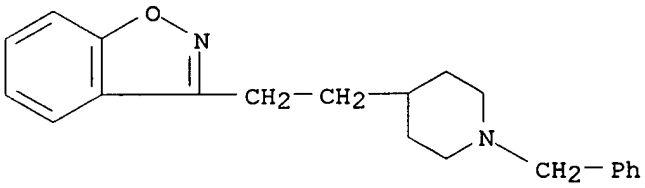


RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

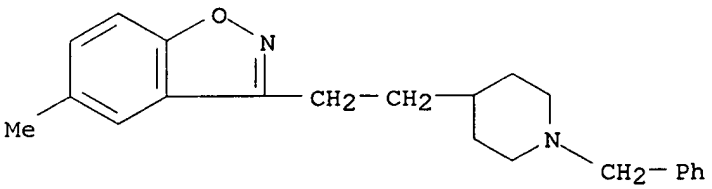
Searched by Barb O'Bryen, STIC 308-4291



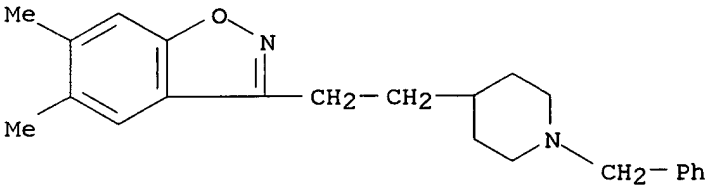
RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



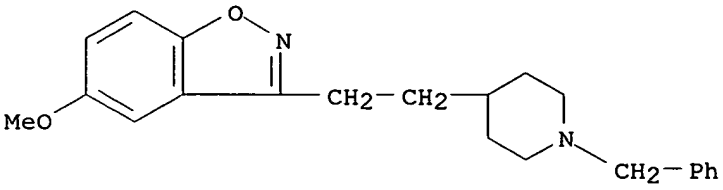
RN 145508-71-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



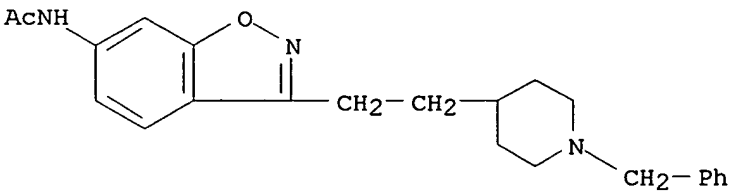
RN 145508-72-1 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



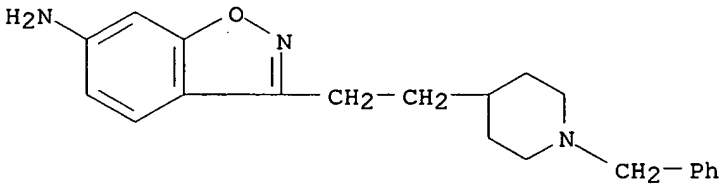
RN 145508-73-2 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



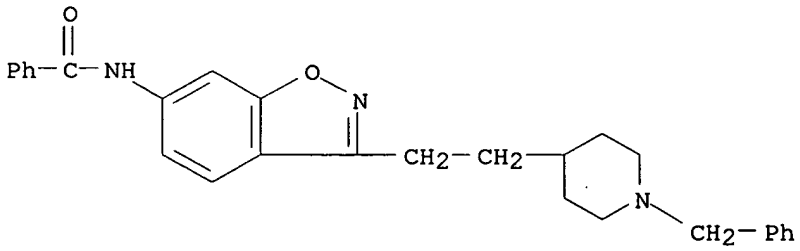
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



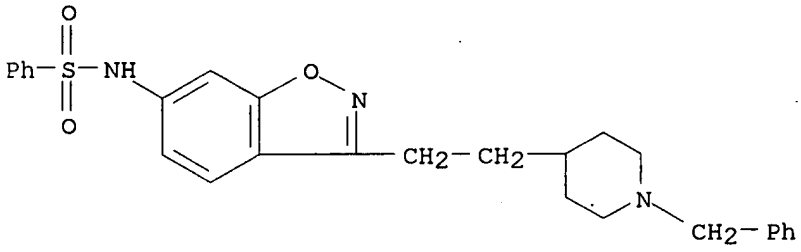
RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



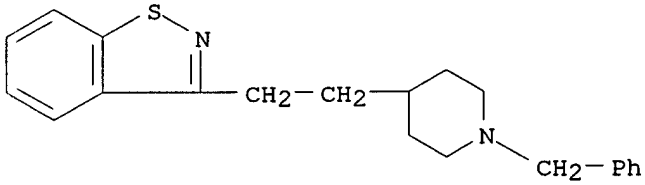
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



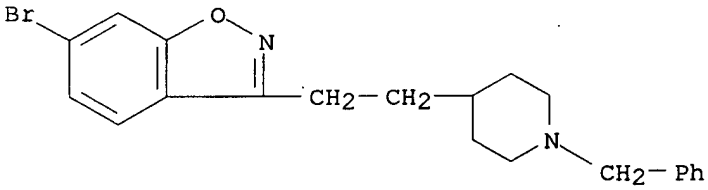
RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



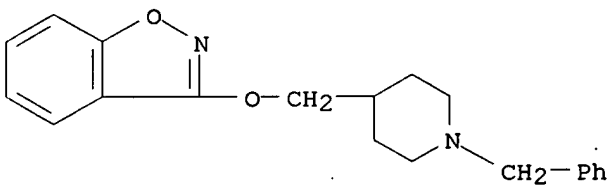
RN 145508-80-1 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



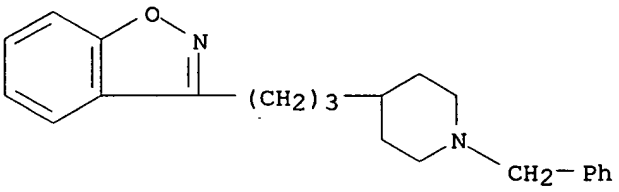
RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-83-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]- (9CI) (CA INDEX NAME)

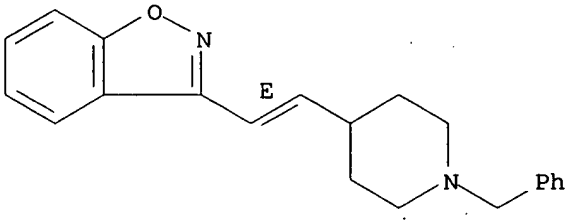


RN 145508-84-5 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



RN 145508-85-6 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]-
(9CI) (CA INDEX NAME)

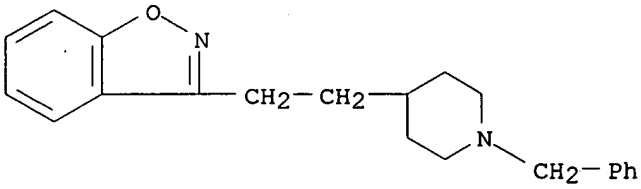
Double bond geometry as shown.



RN 145815-88-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-,
(2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

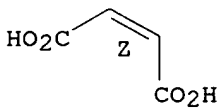
CRN 145508-70-9
CMF C21 H24 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

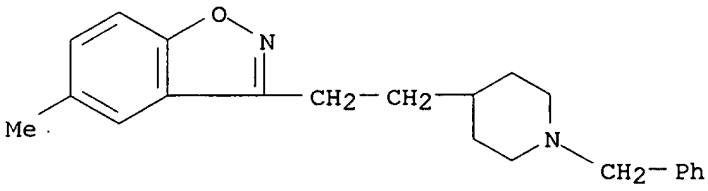


RN 145815-89-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-,

(2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

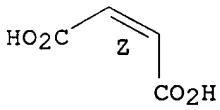
CRN 145508-71-0
CMF C22 H26 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

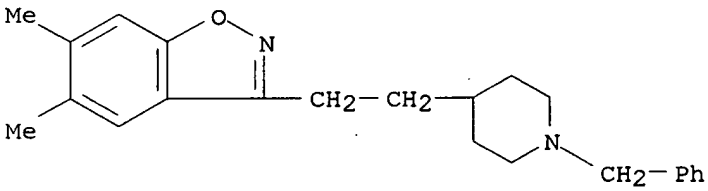
Double bond geometry as shown.



RN 145815-90-3 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

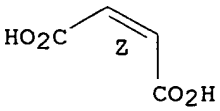
CRN 145508-72-1
CMF C23 H28 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

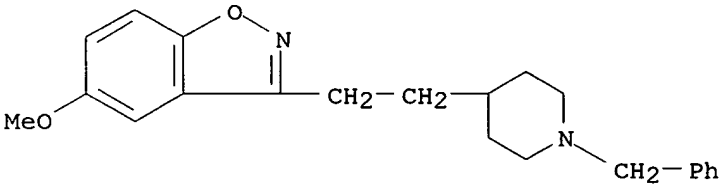
Double bond geometry as shown.



RN 145815-91-4 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

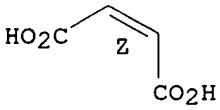
CRN 145508-73-2
CMF C22 H26 N2 O2



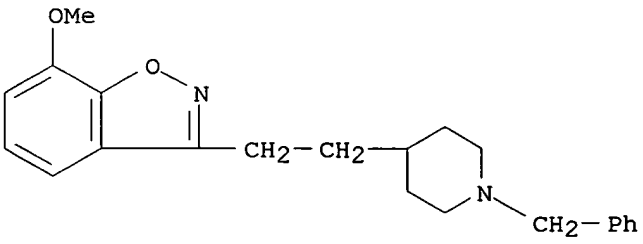
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



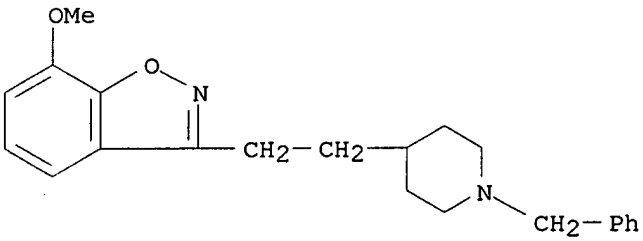
RN 145815-92-5 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-93-6 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

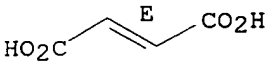
CRN 145815-92-5
CMF C22 H26 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

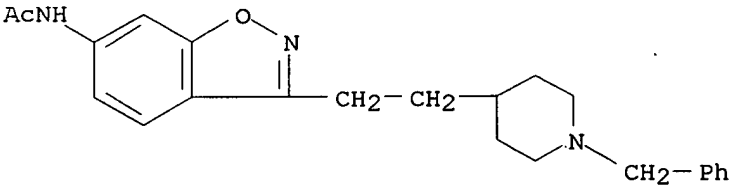
Double bond geometry as shown.



RN 145815-94-7 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

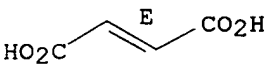
CRN 145508-74-3
CMF C23 H27 N3 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.

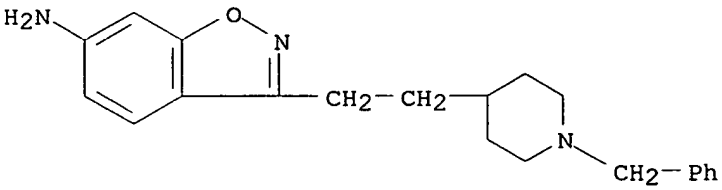


RN 145815-95-8 CAPLUS

CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

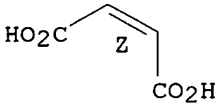
CRN 145508-75-4
CMF C21 H25 N3 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

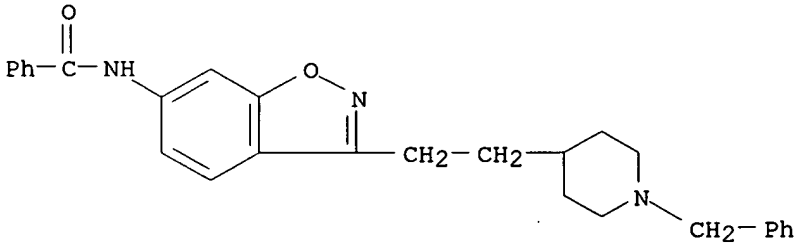
Double bond geometry as shown.



RN 145815-96-9 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-76-5
CMF C28 H29 N3 O2

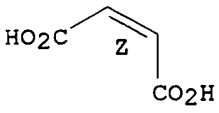


CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

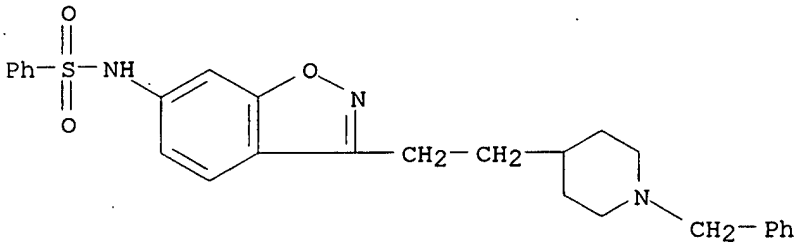
Searched by Barb O'Bryen, STIC 308-4291



RN 145815-97-0 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

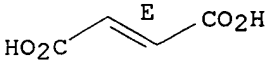
CRN 145508-77-6
CMF C27 H29 N3 O3 S



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

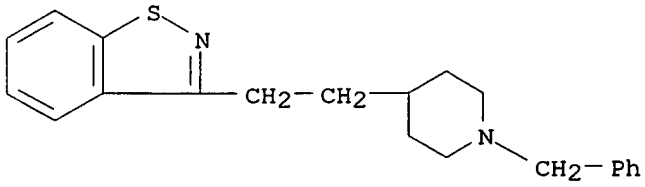
Double bond geometry as shown.



RN 145816-00-8 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

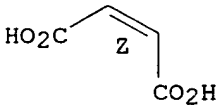
CRN 145508-80-1
CMF C21 H24 N2 S



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

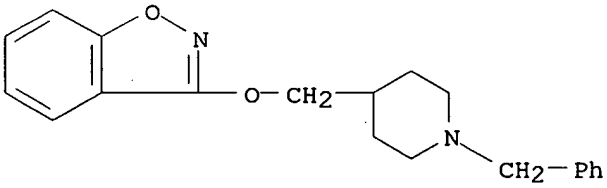
Double bond geometry as shown.



RN 145816-03-1 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

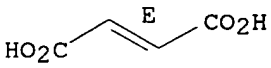
CRN 145508-83-4
CMF C20 H22 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

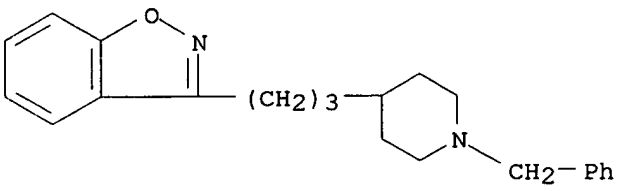
Double bond geometry as shown.



RN 145816-04-2 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

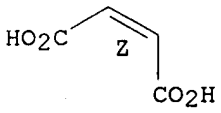
CRN 145508-84-5
CMF C22 H26 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

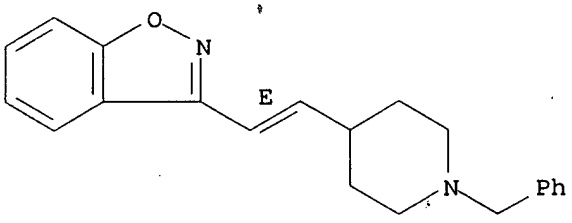


RN 145816-05-3 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-85-6
CMF C21 H22 N2 O
CDES 2:E

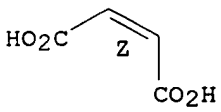
Double bond geometry as shown.



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

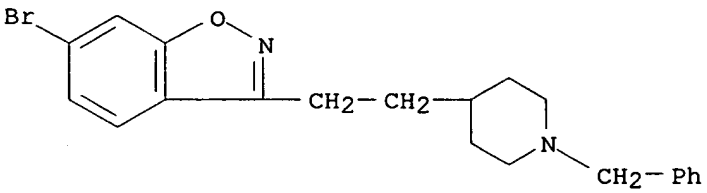
Double bond geometry as shown.



RN 157640-16-9 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (4:3) (9CI) (CA INDEX NAME)

CM 1

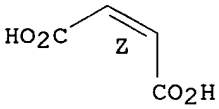
CRN 145508-82-3
CMF C21 H23 Br N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



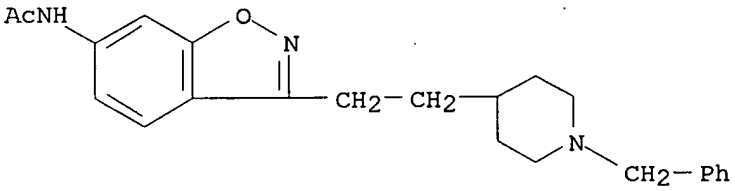
L171 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:307401 CAPLUS
DOCUMENT NUMBER: 122:208557
TITLE: Prediction of the binding site of 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine in acetylcholinesterase by docking studies with the SYSDOC program
AUTHOR(S): Pang, Yuan-Ping; Kozikowski, Alan P.
CORPORATE SOURCE: Neurochemistry Research, Mayo Foundation Medical Education Research, Jacksonville, FL, 32224, USA
SOURCE: J. Comput.-Aided Mol. Des. (1994), 8(6), 683-93
CODEN: JCADEQ; ISSN: 0920-654X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the preceding paper we reported on a docking study with the SYSDOC program for predicting the binding sites of huperzine A in acetylcholinesterase (AChE) [Pang, Y. P. and Kozikowski, A. P., J Comput.-Aided Mol. Design, 8 (1994) 669]. Here we present a prediction of the binding sites of 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine (E2020) in AChE by the same method. E2020 is one of the most potent and selective reversible inhibitors of AChE, and this mol. has puzzled researchers, partly due to its flexible structure, in understanding how it binds to AChE. Based on the results of docking 1320 different conformers of E2020 into 69 different conformers of AChE and on the pharmacol. data reported for E2020 and its analogs, we predict that both the R- and the S-isomer of E2020 span the whole binding cavity of AChE, with the ammonium group interacting mainly with Trp84, Phe330 and

Asp72, the Ph group interacting mainly with Trp84 and Phe330, and the indanone moiety interacting mainly with Tyr70 and Trp279. The topog. of the calcd. E2020 binding sites provides insights into understanding the high potency of E2020 in the inhibition of AChE and provides hints as to possible structural modifications for identifying improved AChE inhibitors as potential therapeutics for the palliative treatment of Alzheimer's disease.

IT **145508-74-3**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(structure-activity relationship of E2020 analogs as inhibitors of acetylcholinesterase)

RN 145508-74-3 CAPLUS

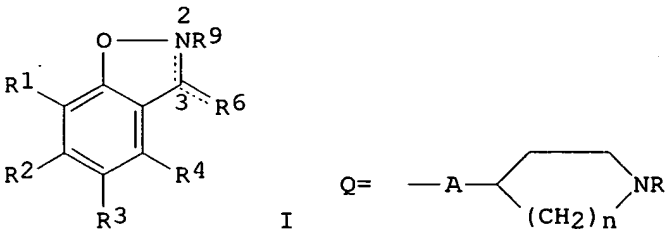
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



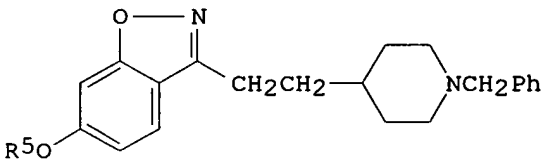
L171 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:560262 CAPLUS
DOCUMENT NUMBER: 119:160262
TITLE: Preparation of benzisoxazole derivatives having centroselective acetylcholine esterase inhibiting activity
INVENTOR(S): Sueoka, Hiroyuki; Murakami, Shu; Takehara, Shuzo
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9304063	A1	19930304	WO 1992-JP1060	19920821
W: CA, HU, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
JP 05320160	A2	19931203	JP 1992-245551	19920821
EP 602242	A1	19940622	EP 1992-918032	19920821
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE				
JP 06041125	A2	19940215	JP 1993-54961	19930219
PRIORITY APPLN. INFO.:			JP 1991-237397	19910822
			JP 1992-100367	19920325
			JP 1992-101707	19920326
			JP 1992-101763	19920326
			JP 1992-112154	19920403
			WO 1992-JP1060	19920821

OTHER SOURCE(S): MARPAT 119:160262
GI



I



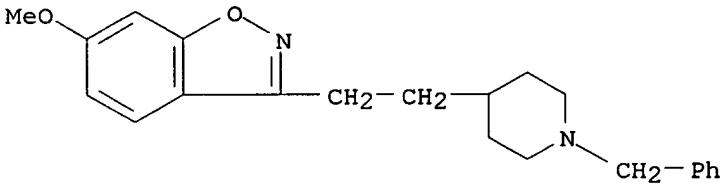
II

AB The title compds. [I; when the bond between the 2- and 3-positions = a single bond, Ra = Q and Rb = O (where R = H, alkyl, alkenyl, cycloalkylalkenyl, phenylalkenyl, naphthylalkyl, or naphthylalkenyl; A = linear or branched alkylene; n = 1-3); when the bond between the 2- and 3-positions = a double bond, Ra is absent and Rb = Q or EQ (where E = O, S); R1-R4 = H, halo, alkyl, alkoxy, Ph, phenylalkyl, phenylalkoxy, PhO, heteroaryl, heteroarylalkyl, heteroaryloxy, acyl, OH, NO2, cyano, etc.], also having a potent affinity for sigma receptor and useful as acetylcholine esterase inhibitors and central nervous system agents, are prepd. Thus, carbamoylation of a hydroxybenzisoxazole deriv. (II; R5 = H) with Me2NCOCl in the presence of NaH in DMF at room temp. to 50.degree. gave II (R5 = CONMe2) which showed IC50 of 0.5 and >10,000 .mu.M against human acetylcholine esterase and butyrylcholine esterase, resp. Approx. 130 I including their salts were prepd.

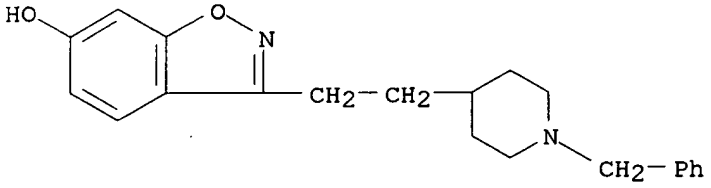
IT **145508-55-0P 145508-57-2P 145508-73-2P**
145508-74-3P 145508-75-4P 145508-76-5P
145815-91-4P 149867-04-9P 149867-05-0P
149867-07-2P 149867-08-3P 149867-10-7P
149867-12-9P 149867-13-0P 149867-14-1P
149867-15-2P 149867-17-4P 149867-18-5P
149867-19-6P 149867-22-1P 149867-23-2P
149867-24-3P 149867-25-4P 149867-26-5P
149867-27-6P 149867-28-7P 149867-30-1P
149867-31-2P 149867-33-4P 149867-34-5P
149867-35-6P 149867-36-7P 149867-38-9P
149867-39-0P 149867-40-3P 149867-41-4P
149867-42-5P 149867-43-6P 149867-44-7P
149867-45-8P 149867-46-9P 149867-47-0P
149867-48-1P 149867-49-2P 149867-51-6P
149867-52-7P 149867-53-8P 149867-54-9P
149867-55-0P 149867-56-1P 149867-58-3P
149867-59-4P 149867-61-8P 149867-63-0P
149896-28-6P 149896-97-9P 149896-99-1P
149897-01-8P 149897-03-0P 149897-04-1P
149897-06-3P 149897-09-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as acetylcholine esterase inhibitor)

RN 145508-55-0 CAPLUS

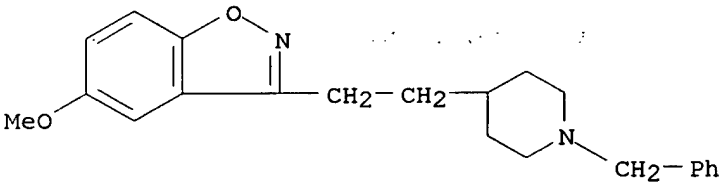
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-(9CI) (CA INDEX NAME)



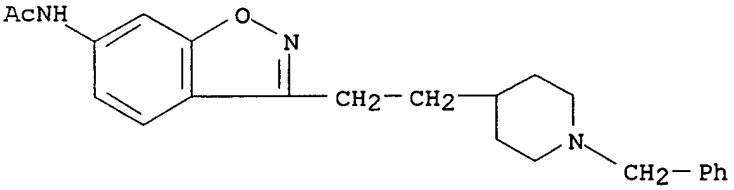
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



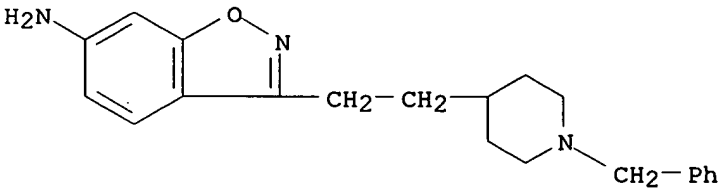
RN 145508-73-2 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



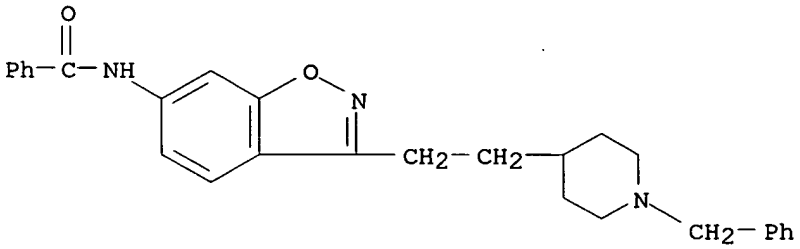
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



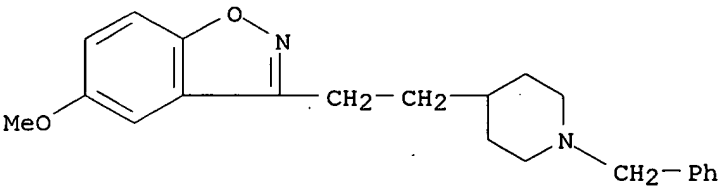
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 145815-91-4 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

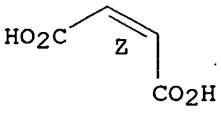
CRN 145508-73-2
CMF C22 H26 N2 O2



CM 2

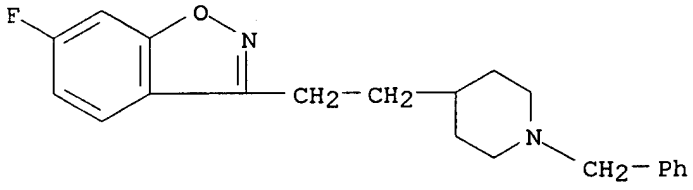
CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



RN 149867-04-9 CAPLUS
CN 1,2-Benzisoxazole, 6-fluoro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-

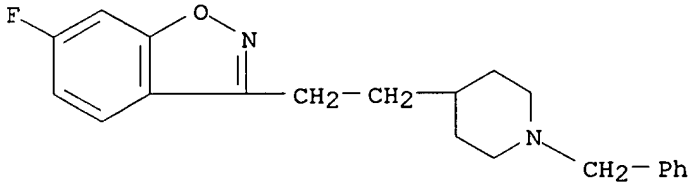
(9CI) (CA INDEX NAME)



RN 149867-05-0 CAPLUS
CN 1,2-Benzisoxazole, 6-fluoro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

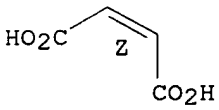
CRN 149867-04-9
CMF C21 H23 F N2 O



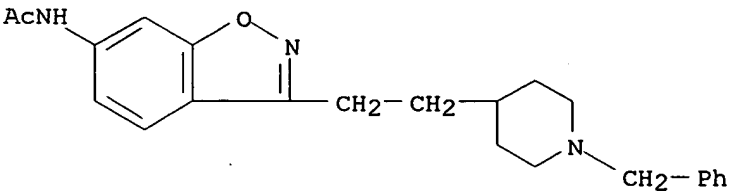
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

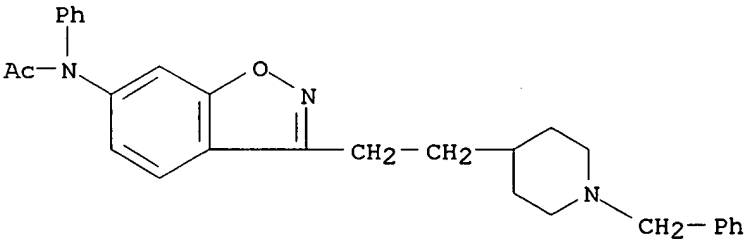


RN 149867-07-2 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, monohydrochloride (9CI) (CA INDEX NAME)

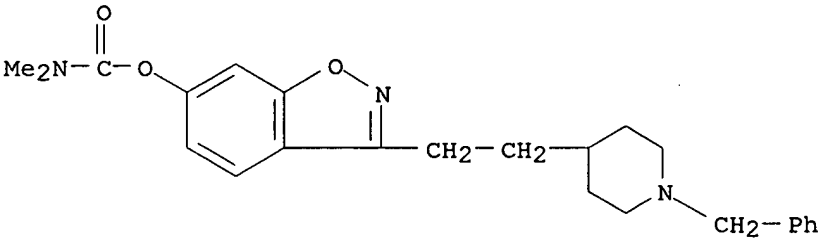


● HCl

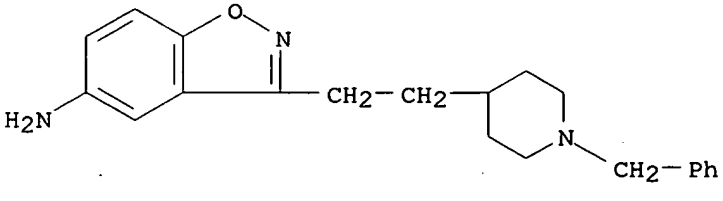
RN 149867-08-3 CAPLUS
CN Acetamide, N-phenyl-N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



RN 149867-10-7 CAPLUS
CN Carbamic acid, dimethyl-, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl ester (9CI) (CA INDEX NAME)

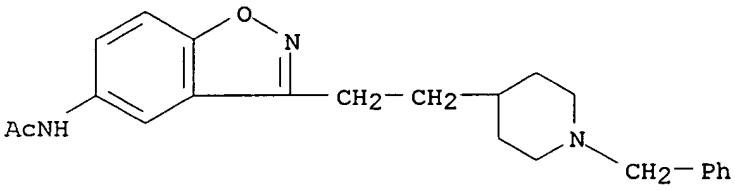


RN 149867-12-9 CAPLUS
CN 1,2-Benzisoxazol-5-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 149867-13-0 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-

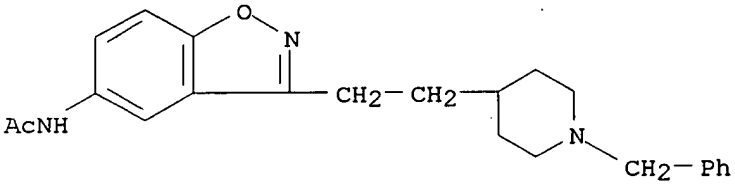
5-yl]- (9CI) (CA INDEX NAME)



RN 149867-14-1 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-5-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

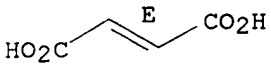
CRN 149867-13-0
CMF C23 H27 N3 O2



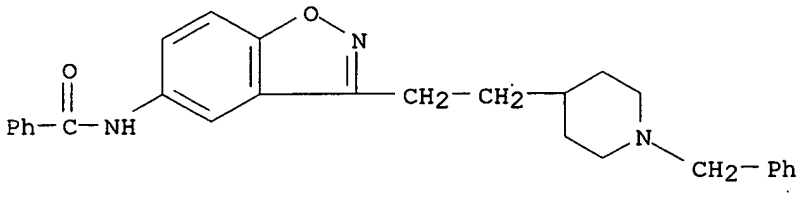
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.

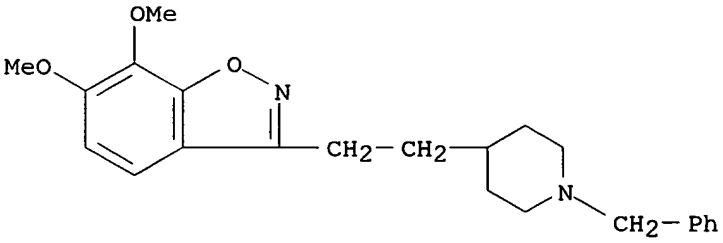


RN 149867-15-2 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-5-yl]- (9CI) (CA INDEX NAME)

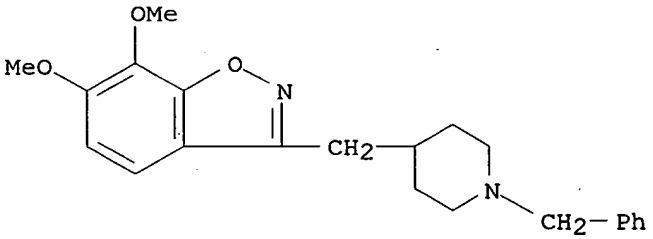


RN 149867-17-4 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291



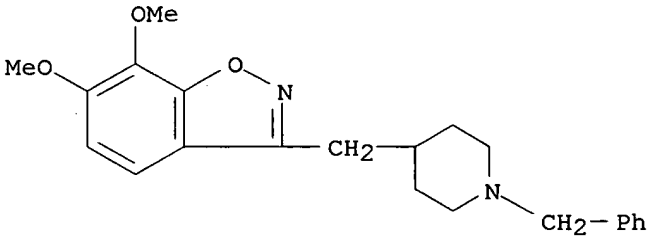
RN 149867-18-5 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[[1-(phenylmethyl)-4-piperidinyl]methyl]- (9CI) (CA INDEX NAME)



RN 149867-19-6 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[[1-(phenylmethyl)-4-piperidinyl]methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

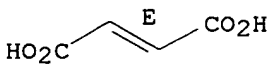
CRN 149867-18-5
CMF C22 H26 N2 O3



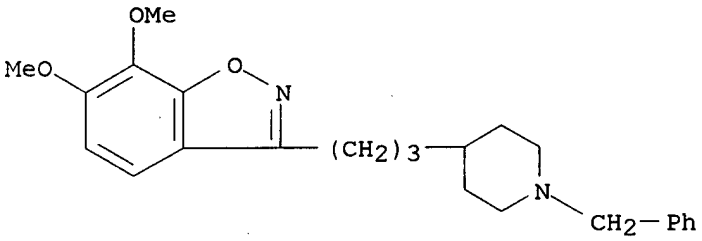
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



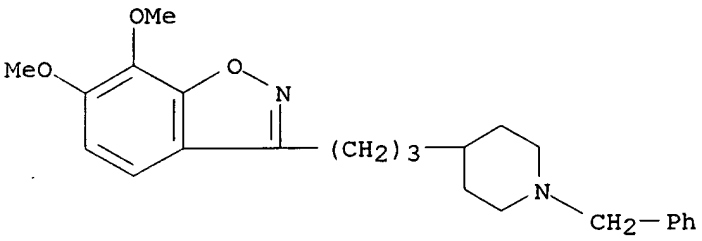
RN 149867-22-1 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



RN 149867-23-2 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

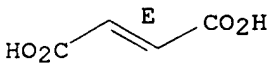
CRN 149867-22-1
CMF C24 H30 N2 O3



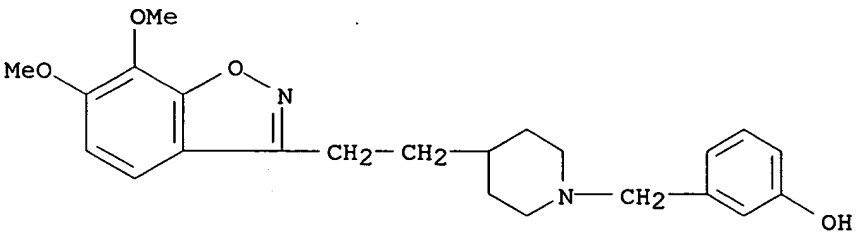
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

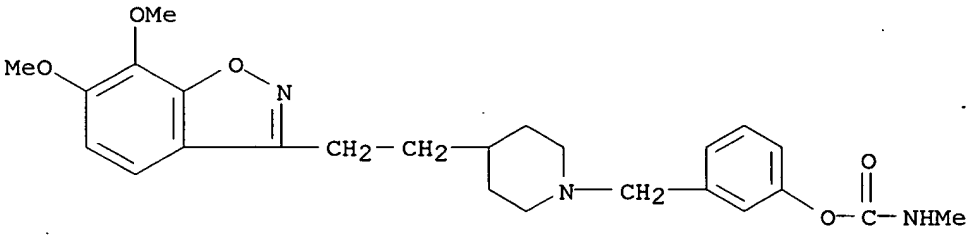
Double bond geometry as shown.



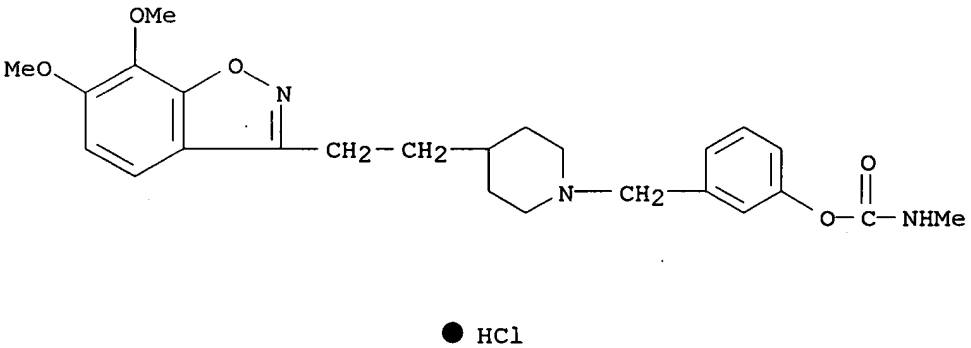
RN 149867-24-3 CAPLUS
CN Phenol, 3-[[4-[2-(6,7-dimethoxy-1,2-benzisoxazol-3-yl)ethyl]-1-piperidinyl]methyl]- (9CI) (CA INDEX NAME)



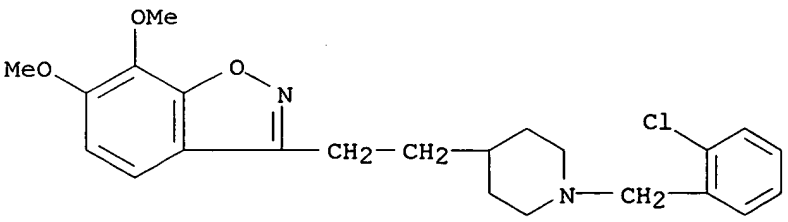
RN 149867-25-4 CAPLUS
CN Phenol, 3-[[4-[2-(6,7-dimethoxy-1,2-benzisoxazol-3-yl)ethyl]-1-piperidinyl]methyl]-, methylcarbamate (ester) (9CI) (CA INDEX NAME)



RN 149867-26-5 CAPLUS
CN Phenol, 3-[[4-[2-(6,7-dimethoxy-1,2-benzisoxazol-3-yl)ethyl]-1-piperidinyl]methyl]-, methylcarbamate (ester), monohydrochloride (9CI) (CA INDEX NAME)



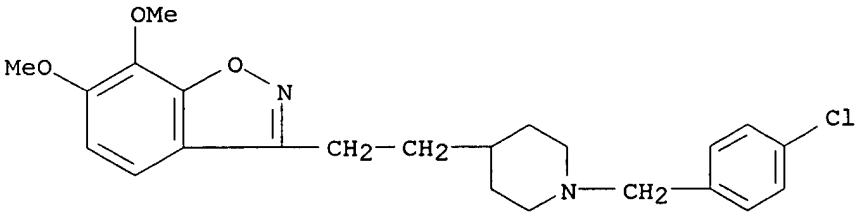
RN 149867-27-6 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-[(2-chlorophenyl)methyl]-4-piperidinyl]ethyl]-6,7-dimethoxy- (9CI) (CA INDEX NAME)



RN 149867-28-7 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

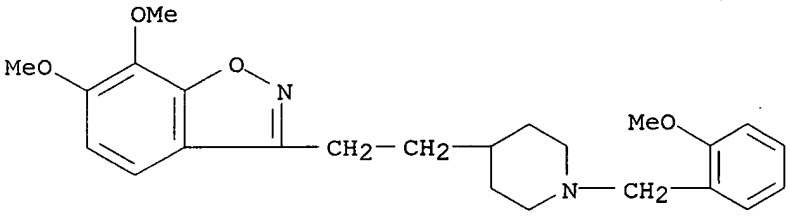
CN 1,2-Benzisoxazole, 3-[2-[1-[(4-chlorophenyl)methyl]-4-piperidinyl]ethyl]-6,7-dimethoxy- (9CI) (CA INDEX NAME)



RN 149867-30-1 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-[(2-methoxyphenyl)methyl]-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

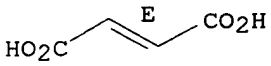
CRN 149867-29-8
CMF C24 H30 N2 O4



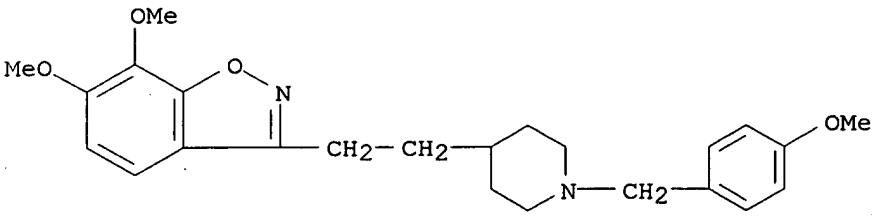
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



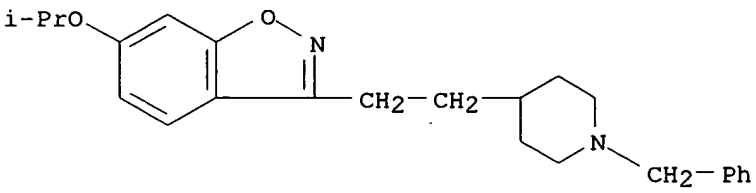
RN 149867-31-2 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-[(4-methoxyphenyl)methyl]-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 149867-33-4 CAPLUS
CN 1,2-Benzisoxazole, 6-(1-methylethoxy)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

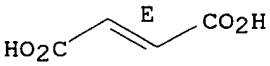
CRN 149867-32-3
CMF C24 H30 N2 O2



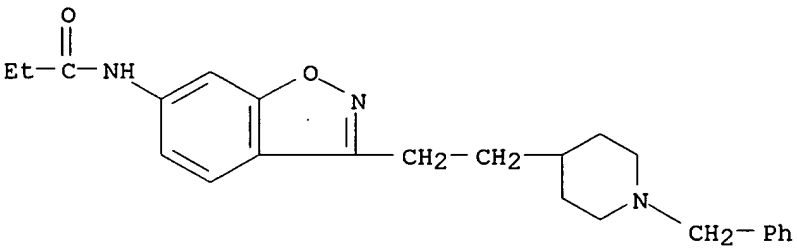
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

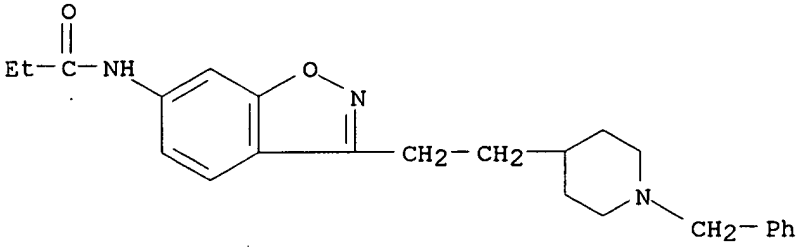
Double bond geometry as shown.



RN 149867-34-5 CAPLUS
CN Propanamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)

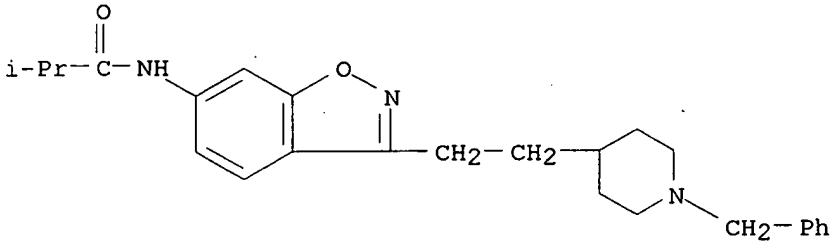


RN 149867-35-6 CAPLUS
CN Propanamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, monohydrochloride (9CI) (CA INDEX NAME)

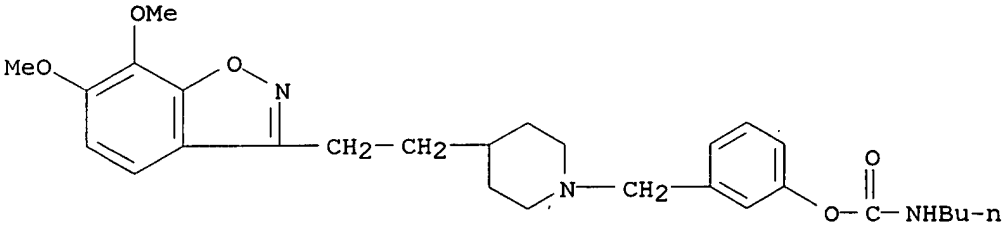


● HCl

RN 149867-36-7 CAPLUS
CN Propanamide, 2-methyl-N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)

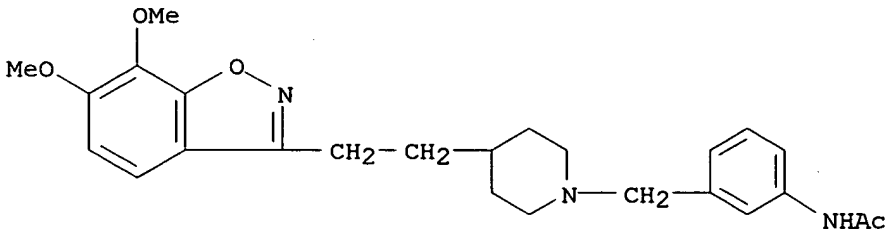


RN 149867-38-9 CAPLUS
CN Carbamic acid, butyl-, 3-[[4-[2-(6,7-dimethoxy-1,2-benzisoxazol-3-yl)ethyl]-1-piperidinyl]methyl]phenyl ester, monohydrochloride (9CI) (CA INDEX NAME)

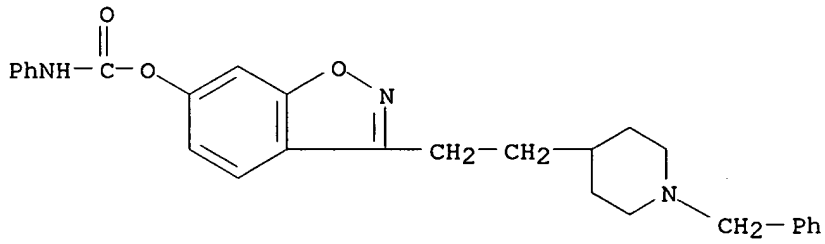


● HCl

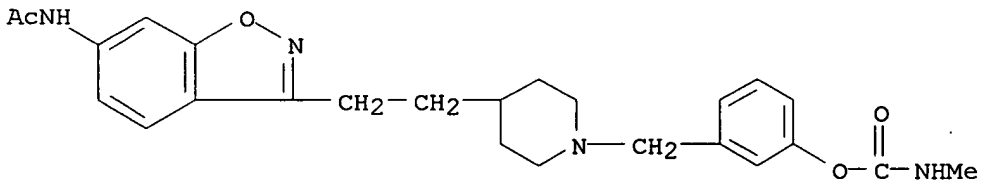
RN 149867-39-0 CAPLUS
CN Acetamide, N-[3-[[4-[2-(6,7-dimethoxy-1,2-benzisoxazol-3-yl)ethyl]-1-piperidinyl]methyl]phenyl]- (9CI) (CA INDEX NAME)



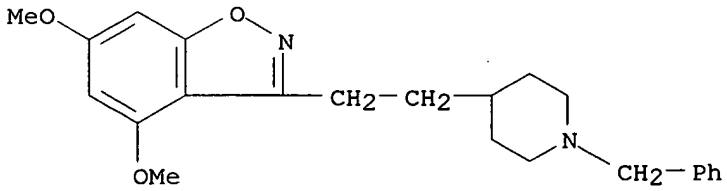
RN 149867-40-3 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, phenylcarbamate (ester) (9CI) (CA INDEX NAME)



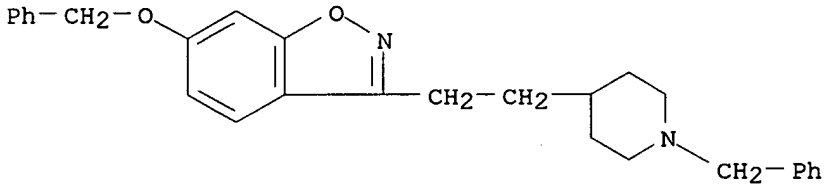
RN 149867-41-4 CAPLUS
CN Acetamide, N-[3-[2-[1-[[3-[[(methylamino)carbonyl]oxy]phenyl]methyl]-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



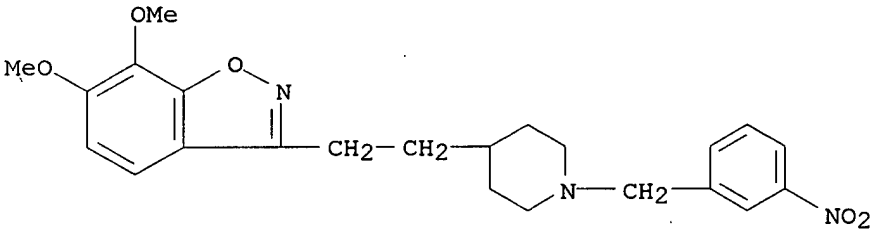
RN 149867-42-5 CAPLUS
CN 1,2-Benzisoxazole, 4,6-dimethoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



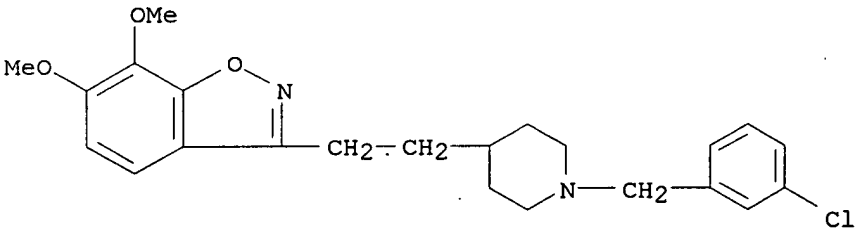
RN 149867-43-6 CAPLUS
CN 1,2-Benzisoxazole, 6-(phenylmethoxy)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



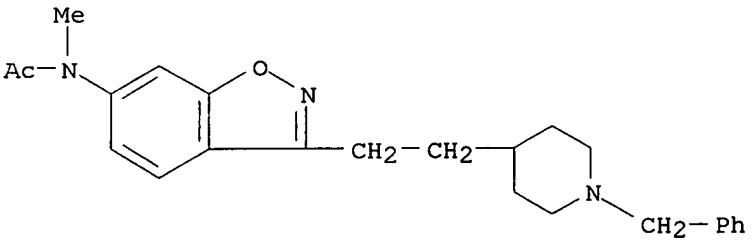
RN 149867-44-7 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-[(3-nitrophenyl)methyl]-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



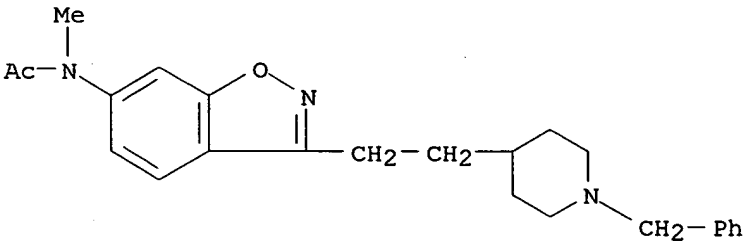
RN 149867-45-8 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-[(3-chlorophenyl)methyl]-4-piperidinyl]ethyl]-6,7-dimethoxy- (9CI) (CA INDEX NAME)



RN 149867-46-9 CAPLUS
CN Acetamide, N-methyl-N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)

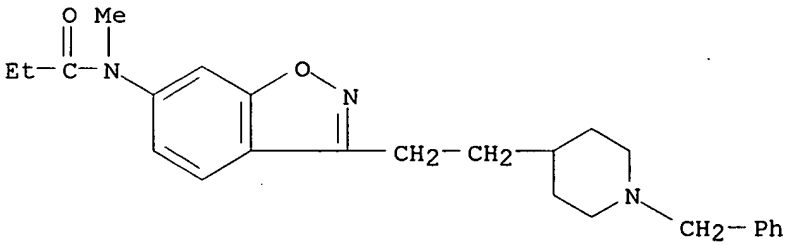


RN 149867-47-0 CAPLUS
CN Acetamide, N-methyl-N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, monohydrochloride (9CI) (CA INDEX NAME)

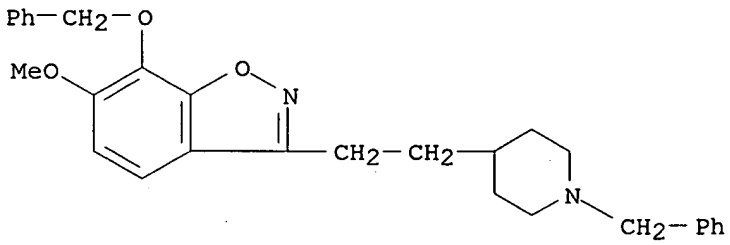


● HCl

RN 149867-48-1 CAPLUS
CN Propanamide, N-methyl-N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



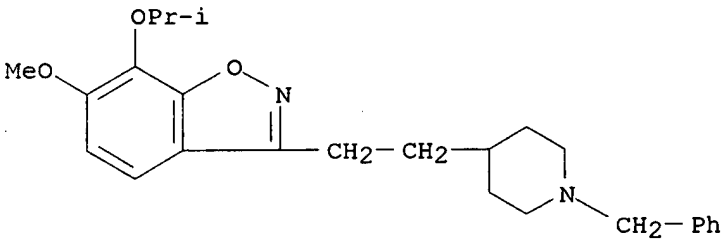
RN 149867-49-2 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-7-(phenylmethoxy)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 149867-51-6 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-7-(1-methylethoxy)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

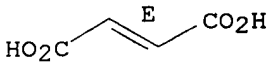
CRN 149867-50-5
CMF C25 H32 N2 O3



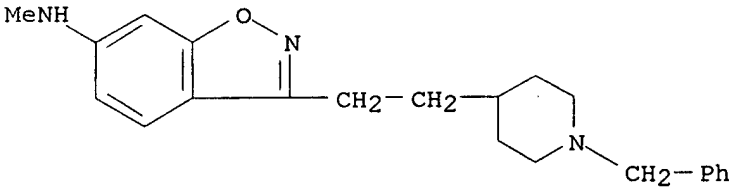
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



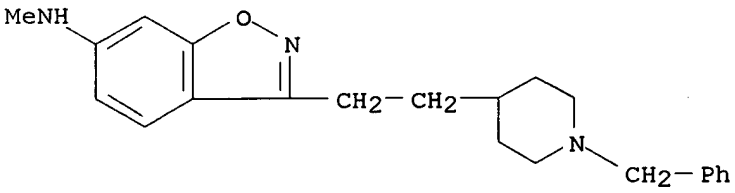
RN 149867-52-7 CAPLUS
CN 1,2-Benzisoxazol-6-amine, N-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 149867-53-8 CAPLUS
CN 1,2-Benzisoxazol-6-amine, N-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 149867-52-7
CMF C22 H27 N3 O

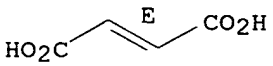


CM 2

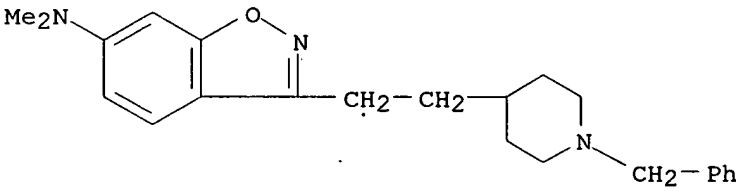
CRN 110-17-8

CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



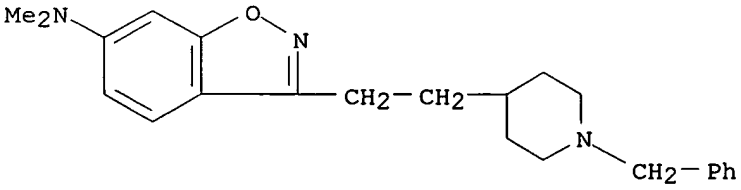
RN 149867-54-9 CAPLUS
CN 1,2-Benzisoxazol-6-amine, N,N-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 149867-55-0 CAPLUS
CN 1,2-Benzisoxazol-6-amine, N,N-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

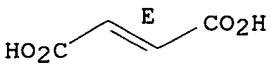
CRN 149867-54-9
CMF C23 H29 N3 O



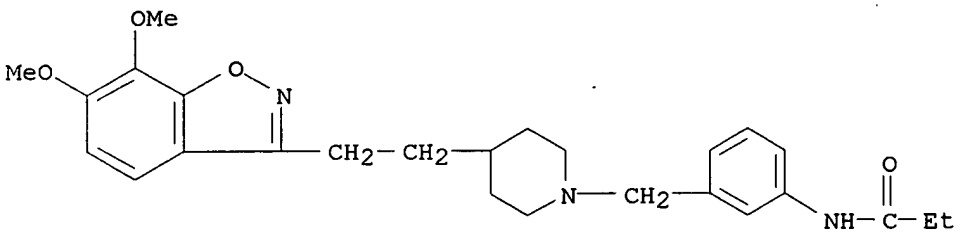
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

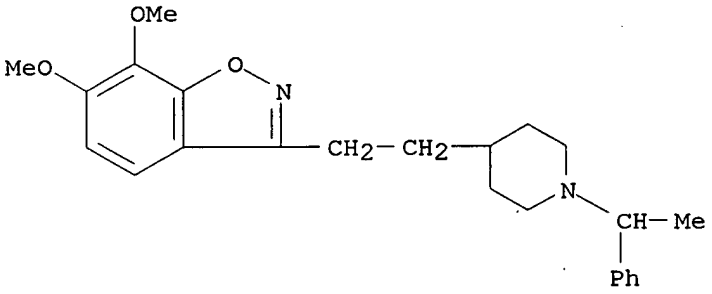
Double bond geometry as shown.



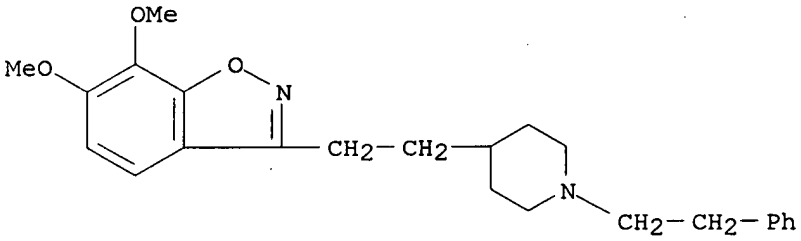
RN 149867-56-1 CAPLUS
CN Propanamide, N-[3-[[4-[2-(6,7-dimethoxy-1,2-benzisoxazol-3-yl)ethyl]-1-piperidinyl]methyl]phenyl]- (9CI) (CA INDEX NAME)



RN 149867-58-3 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-(1-phenylethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



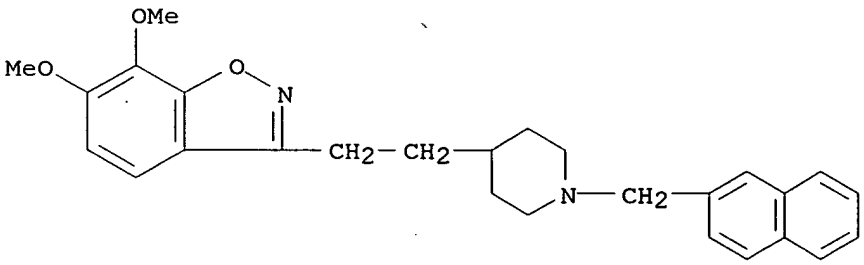
RN 149867-59-4 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-(2-phenylethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 149867-61-8 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-(2-naphthalenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

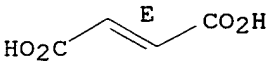
CRN 149867-60-7
CMF C27 H30 N2 O3



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

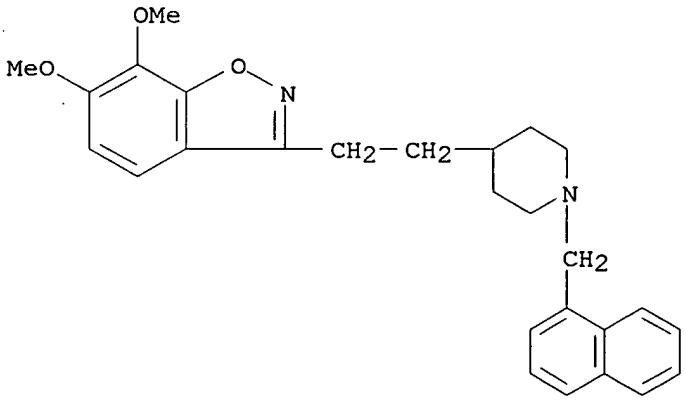
Double bond geometry as shown.



RN 149867-63-0 CAPLUS
CN 1,2-Benzisoxazole, 6,7-dimethoxy-3-[2-[1-(1-naphthalenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

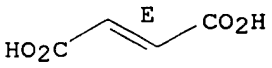
CRN 149867-62-9
CMF C27 H30 N2 O3



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

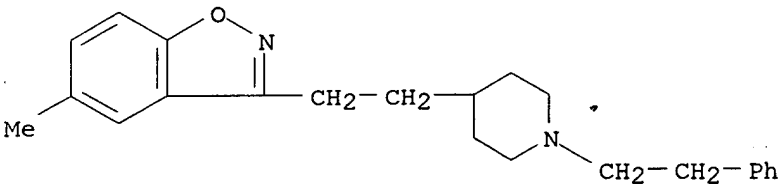
Double bond geometry as shown.



RN 149896-28-6 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(2-phenylethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

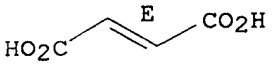
CRN 149896-27-5
CMF C23 H28 N2 O



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

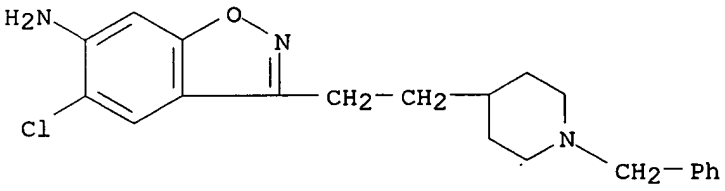
Double bond geometry as shown.



RN 149896-97-9 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 5-chloro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

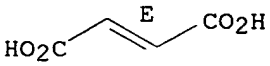
CRN 149896-96-8
CMF C21 H24 Cl N3 O



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

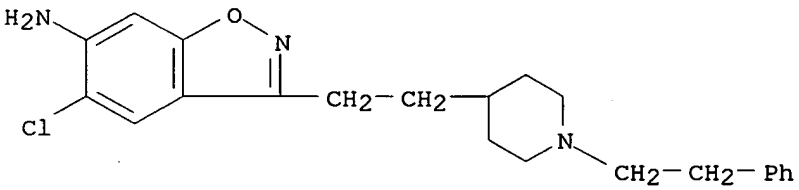
Double bond geometry as shown.



RN 149896-99-1 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 5-chloro-3-[2-[1-(2-phenylethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

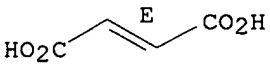
CRN 149896-98-0
CMF C22 H26 Cl N3 O



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

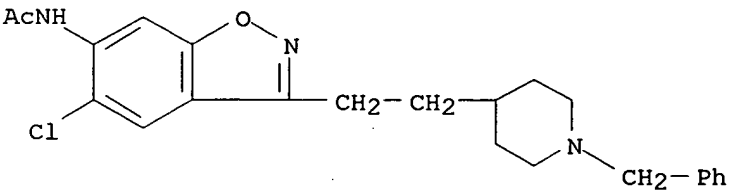
Double bond geometry as shown.



RN 149897-01-8 CAPLUS
CN Acetamide, N-[5-chloro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 149897-00-7
CMF C23 H26 Cl N3 O2

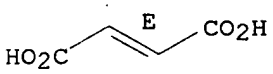


CM 2

CRN 110-17-8

CMF C4 H4 O4
CDES 2:E

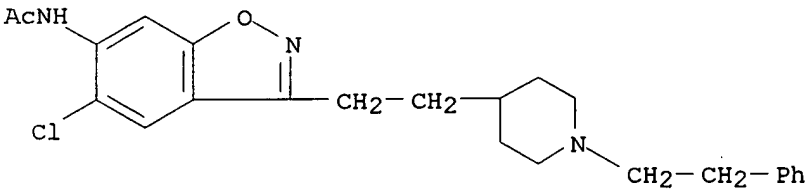
Double bond geometry as shown.



RN 149897-03-0 CAPLUS
CN Acetamide, N-[5-chloro-3-[2-[1-(2-phenylethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

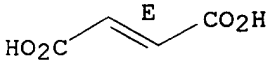
CRN 149897-02-9
CMF C24 H28 Cl N3 O2



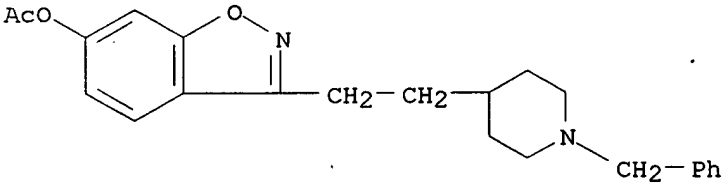
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



RN 149897-04-1 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, acetate (ester) (9CI) (CA INDEX NAME)

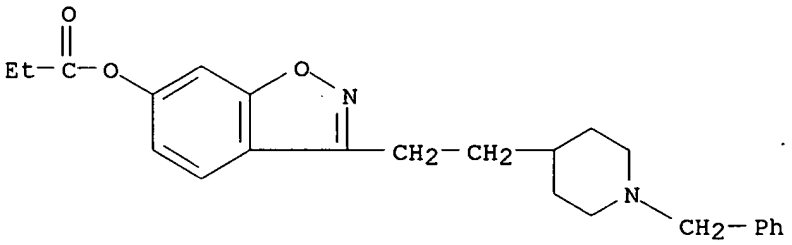


RN 149897-06-3 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, propanoate (ester), (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 149897-05-2

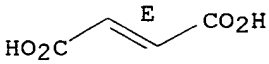
CMF C24 H28 N2 O3



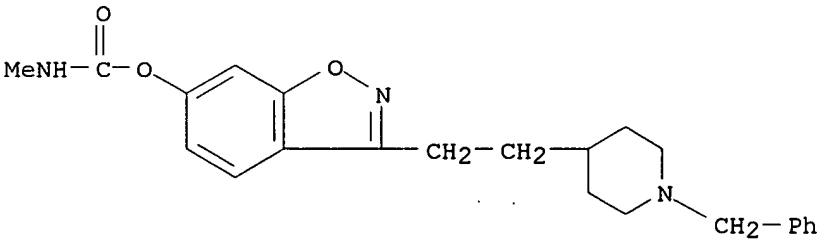
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



RN 149897-09-6 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, methylcarbamate (ester) (9CI) (CA INDEX NAME)



L171 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:80924 CAPLUS
DOCUMENT NUMBER: 118:80924
TITLE: Heterocyclic-cyclic amine derivatives, [(1-benzyl-4-piperidinyl)alkyl]benzisoxazoles and heteroaryl analogs, a method for their preparation and their use as cholinesterase inhibitors
INVENTOR(S): Villalobos, Anabella; Nagel, Arthur Adam; Chen, Yuhpyng Liang
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 9217475	A1	19921015	WO 1992-US1605	19920309
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RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
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AU 658194	B2	19950406		
JP 06500794	T2	19940127	JP 1992-510182	19920309
BR 9205811	A	19940628	BR 1992-5811	19920309
EP 646115	A1	19950405	EP 1992-921695	19920309
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PL 170567	B1	19970131	PL 1992-300711	19920309
PL 171915	B1	19970630	PL 1992-313811	19920309
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JP 2000154185	A2	20000606	JP 1999-368302	19920309
IL 101327	A1	19980615	IL 1992-101327	19920322
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PRIORITY APPLN. INFO.:

US 1991-676918	19910328
JP 1992-510182	19920309
JP 1997-52097	19920309
WO 1992-US1605	19920309
IL 1992-101327	19920322

OTHER SOURCE(S): CASREACT 118:80924; MARPAT 118:80924

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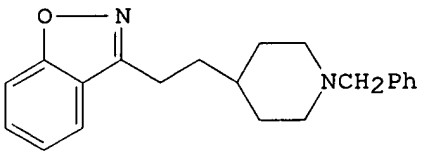

I

AB Heterocyclic amine derivs., such as [(1-benzyl-4-piperidinyl)alkyl]benzisoxazoles, -isoquinolines, -benzisothiazoles, -quinazolines and analogs and derivs. thereof are claimed. These compds. are useful as memory enhancers and for the treatment or prevention of Alzheimer's disease; these compds. are cholinesterase inhibitors (no data). Thus 3-[2-[(1-benzyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole (I) was prepd. from Et isonipecotate and 3-methyl-1,2-benzisoxazole in a multistep synthesis. The biol. activity of I was not tested.

IT **145508-55-0P 145508-56-1P 145508-57-2P**
145508-58-3P 145508-59-4P 145508-64-1P
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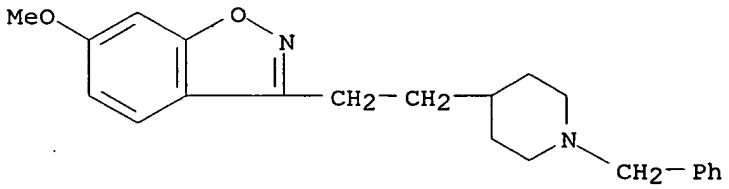
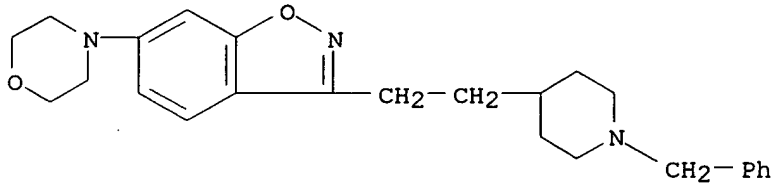
145816-03-1P 145816-04-2P 145816-05-3P
145816-07-5P 145816-08-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as memory enhancer and for treatment of Alzheimer's disease (cholinesterase inhibitor))

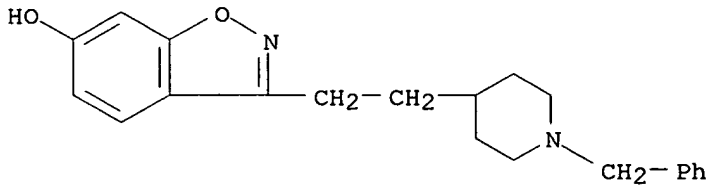
RN 145508-55-0 CAPLUS
CN 1,2-Benzisoxazole, 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



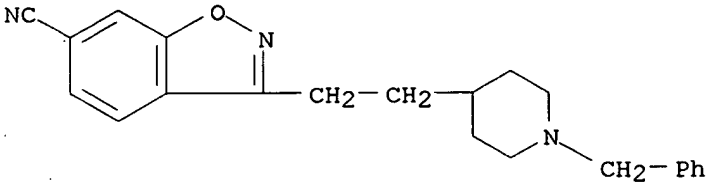
RN 145508-56-1 CAPLUS
CN 1,2-Benzisoxazole, 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



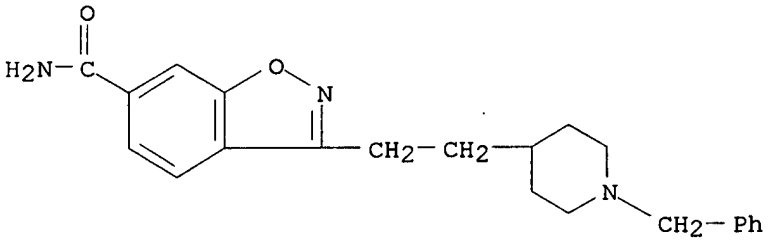
RN 145508-57-2 CAPLUS
CN 1,2-Benzisoxazol-6-ol, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



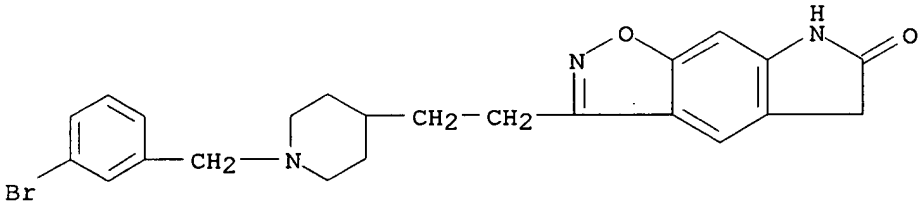
RN 145508-58-3 CAPLUS
CN 1,2-Benzisoxazole-6-carbonitrile, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



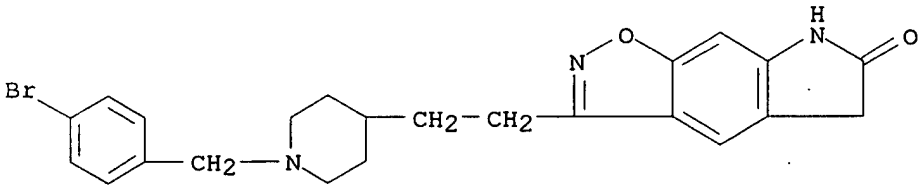
RN 145508-59-4 CAPLUS
CN 1,2-Benzisoxazole-6-carboxamide, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



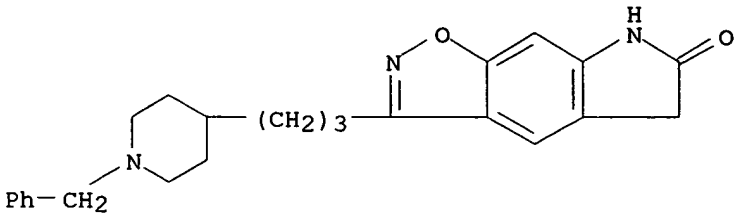
RN 145508-64-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(3-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)



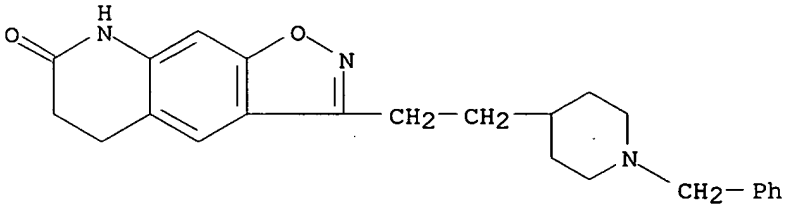
RN 145508-65-2 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 3-[2-[1-[(4-bromophenyl)methyl]-4-piperidinyl]ethyl]-5,7-dihydro- (9CI) (CA INDEX NAME)



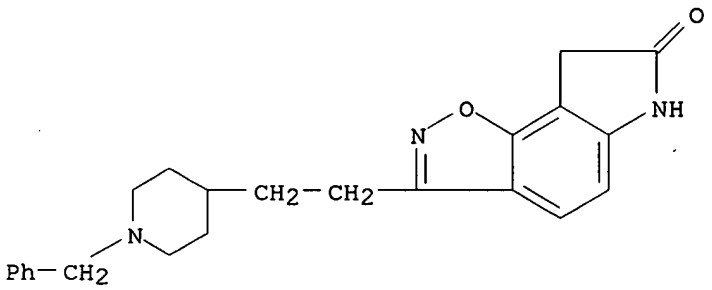
RN 145508-66-3 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)



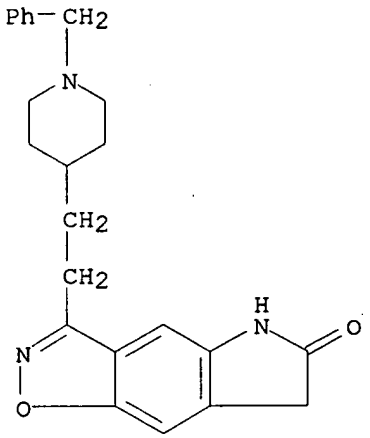
RN 145508-67-4 CAPLUS
CN Isoxazolo[4,5-g]quinolin-7(6H)-one, 5,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



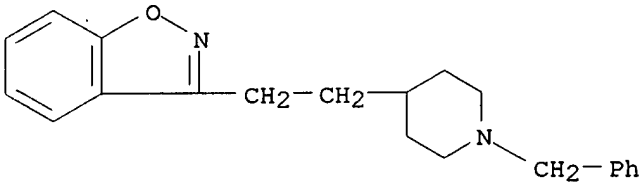
RN 145508-68-5 CAPLUS
CN 7H-Pyrrolo[2,3-g]-1,2-benzisoxazol-7-one, 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



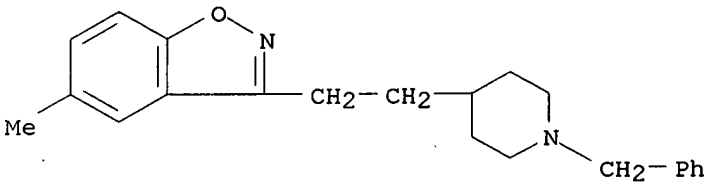
RN 145508-69-6 CAPLUS
CN 6H-Pyrrolo[2,3-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



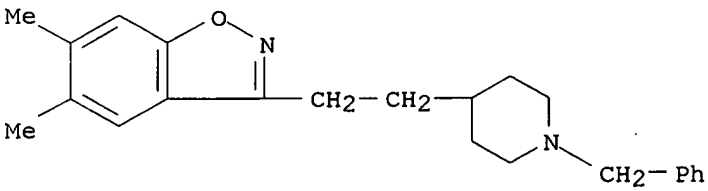
RN 145508-70-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-71-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



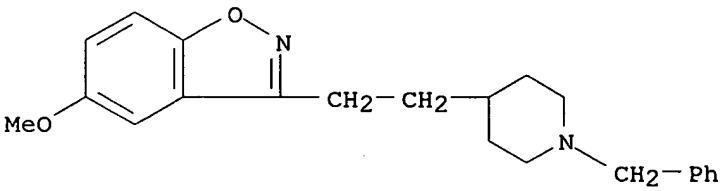
RN 145508-72-1 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



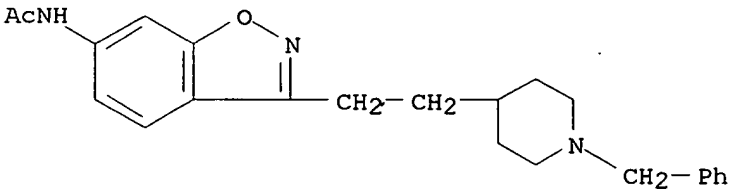
RN 145508-73-2 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

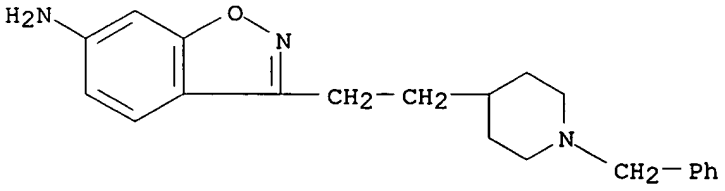
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



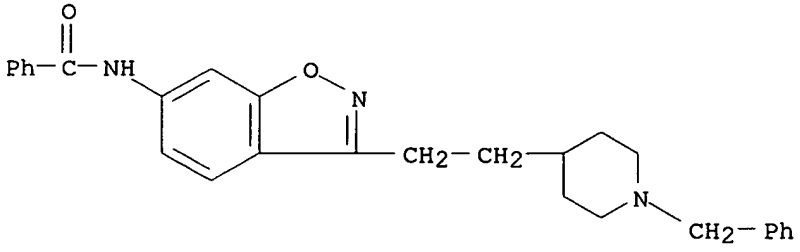
RN 145508-74-3 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



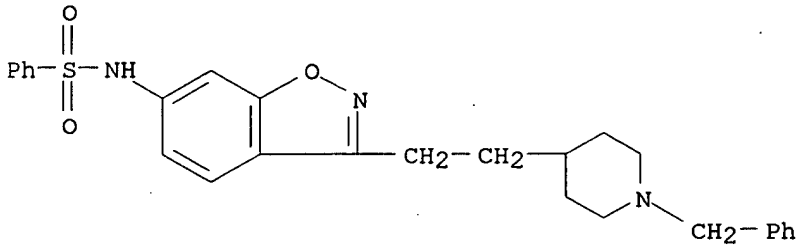
RN 145508-75-4 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



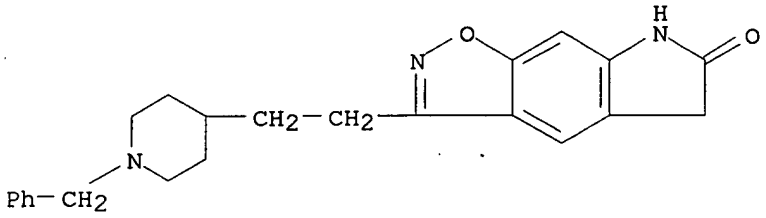
RN 145508-76-5 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



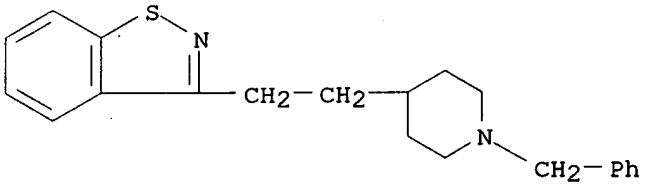
RN 145508-77-6 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]- (9CI) (CA INDEX NAME)



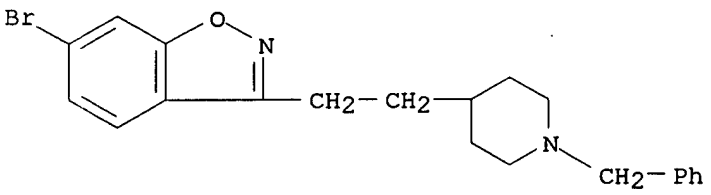
RN 145508-78-7 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



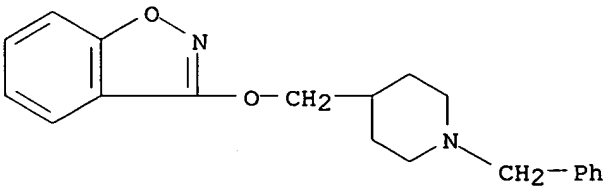
RN 145508-80-1 CAPLUS
CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



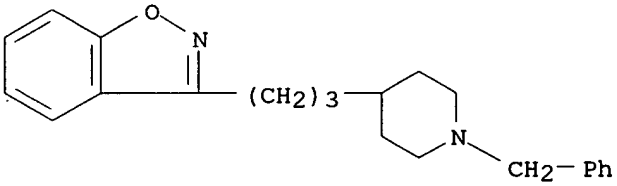
RN 145508-82-3 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145508-83-4 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]- (9CI) (CA INDEX NAME)

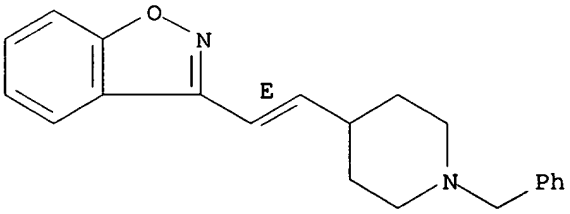


RN 145508-84-5 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]- (9CI) (CA INDEX NAME)

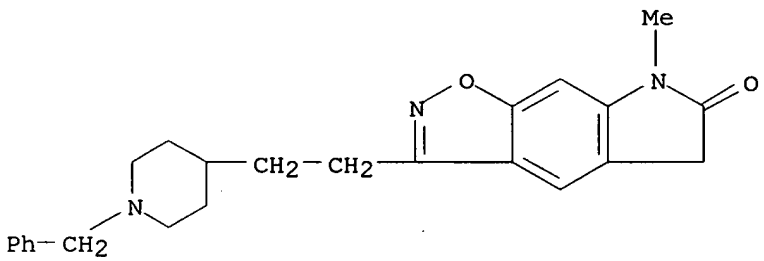


RN 145508-85-6 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]- (9CI) (CA INDEX NAME)

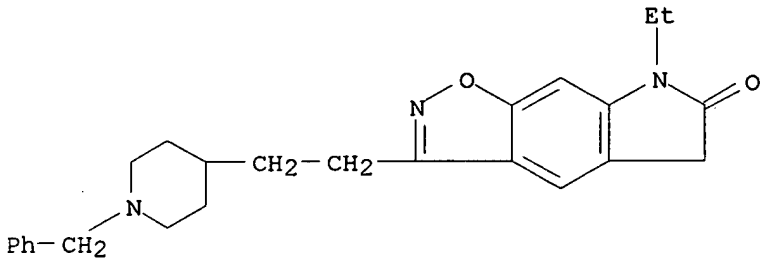
Double bond geometry as shown.



RN 145508-87-8 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



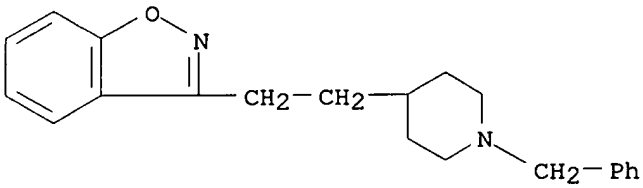
RN 145508-88-9 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



RN 145815-88-9 CAPLUS
CN 1,2-Benzisoxazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

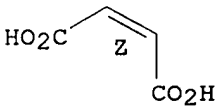
CRN 145508-70-9
CMF C21 H24 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

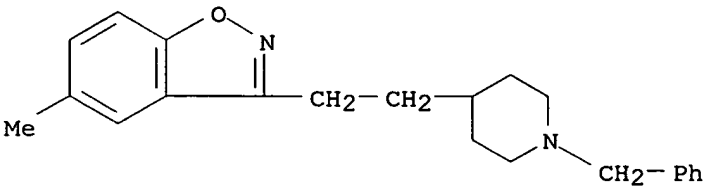
Double bond geometry as shown.



RN 145815-89-0 CAPLUS
CN 1,2-Benzisoxazole, 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

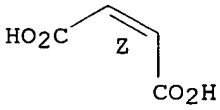
CRN 145508-71-0
CMF C22 H26 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

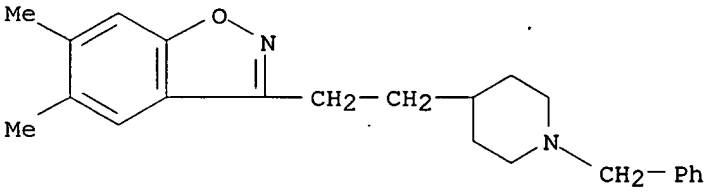
Double bond geometry as shown.



RN 145815-90-3 CAPLUS
CN 1,2-Benzisoxazole, 5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

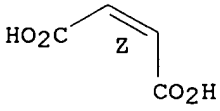
CRN 145508-72-1
CMF C23 H28 N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

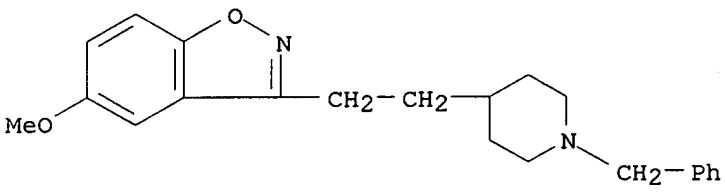


RN 145815-91-4 CAPLUS
CN 1,2-Benzisoxazole, 5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

CM 1

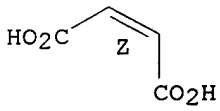
CRN 145508-73-2
CMF C22 H26 N2 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

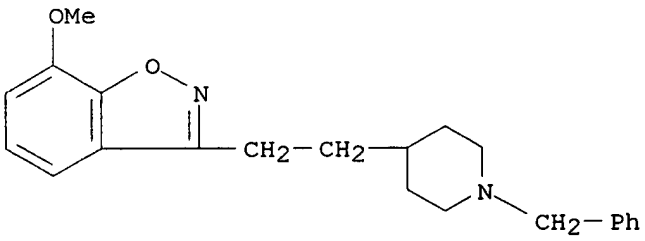
Double bond geometry as shown.



RN 145815-93-6 CAPLUS
CN 1,2-Benzisoxazole, 7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

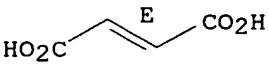
CRN 145815-92-5
CMF C22 H26 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

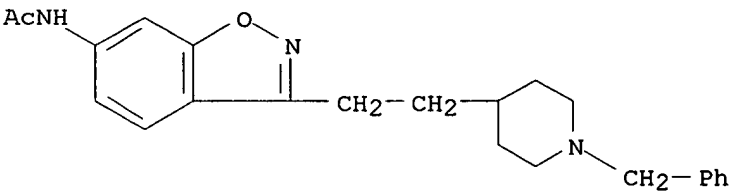
Double bond geometry as shown.



RN 145815-94-7 CAPLUS
CN Acetamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

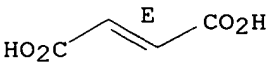
CRN 145508-74-3
CMF C23 H27 N3 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

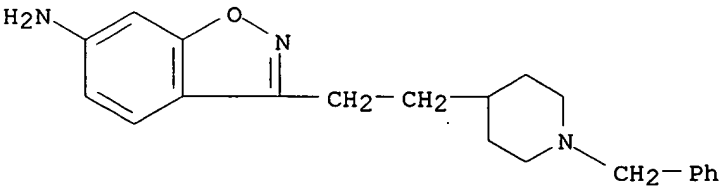
Double bond geometry as shown.



RN 145815-95-8 CAPLUS
CN 1,2-Benzisoxazol-6-amine, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

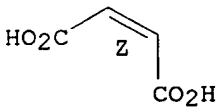
CRN 145508-75-4
CMF C21 H25 N3 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

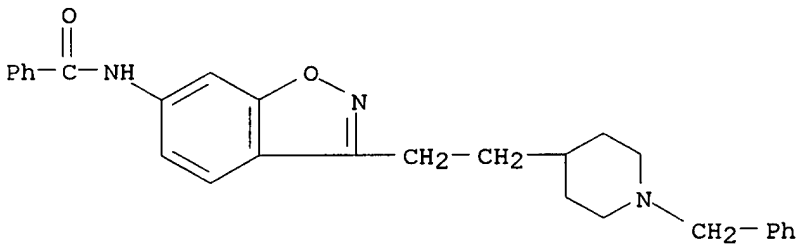
Double bond geometry as shown.



RN 145815-96-9 CAPLUS
CN Benzamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

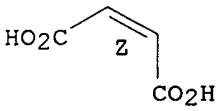
CRN 145508-76-5
CMF C28 H29 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

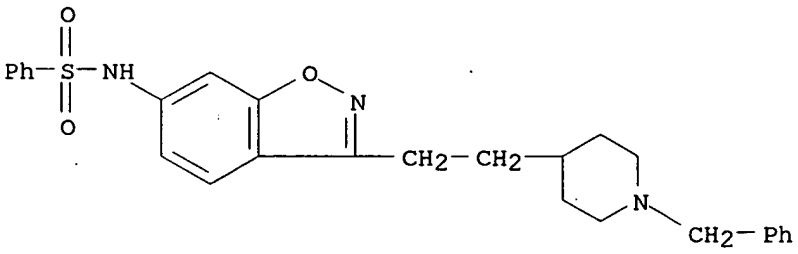
Double bond geometry as shown.



RN 145815-97-0 CAPLUS
CN Benzenesulfonamide, N-[3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazol-6-yl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

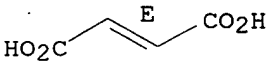
CRN 145508-77-6
CMF C27 H29 N3 O3 S



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

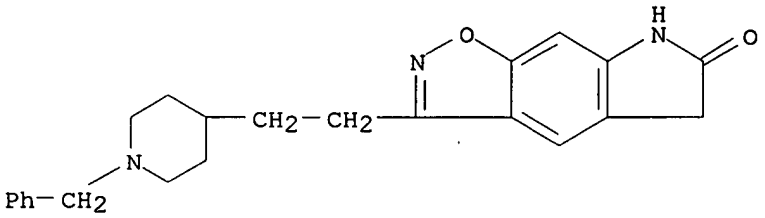
Double bond geometry as shown.



RN 145815-98-1 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

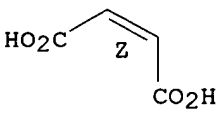
CRN 145508-78-7
CMF C23 H25 N3 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

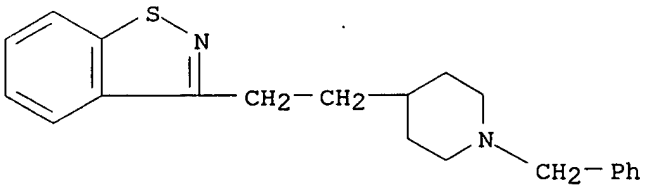


RN 145816-00-8 CAPLUS

CN 1,2-Benzisothiazole, 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

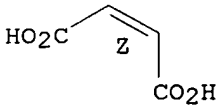
CRN 145508-80-1
CMF C21 H24 N2 S



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

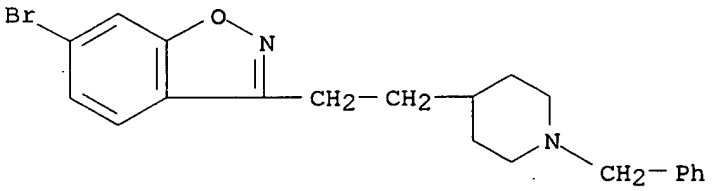
Double bond geometry as shown.



RN 145816-02-0 CAPLUS
CN 1,2-Benzisoxazole, 6-bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

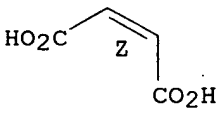
CRN 145508-82-3
CMF C21 H23 Br N2 O



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

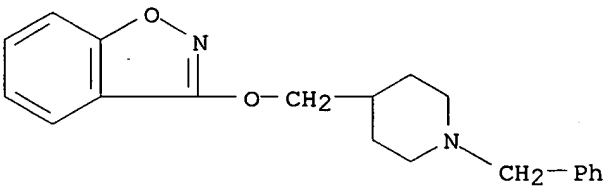
Double bond geometry as shown.



RN 145816-03-1 CAPLUS
CN 1,2-Benzisoxazole, 3-[[1-(phenylmethyl)-4-piperidinyl]methoxy]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

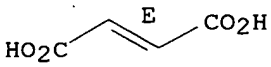
CRN 145508-83-4
CMF C20 H22 N2 O2



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

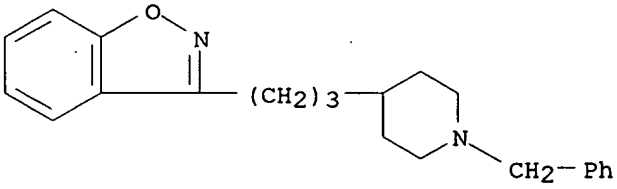
Double bond geometry as shown.



RN 145816-04-2 CAPLUS
CN 1,2-Benzisoxazole, 3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-84-5
CMF C22 H26 N2 O

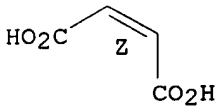


CM 2

CRN 110-16-7

CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

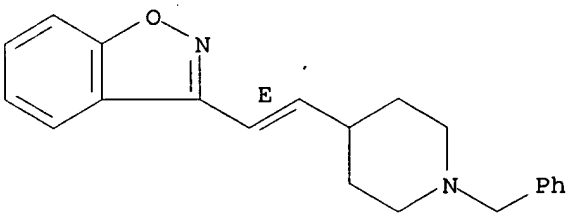


RN 145816-05-3 CAPLUS
CN 1,2-Benzisoxazole, 3-[(1E)-2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 145508-85-6
CMF C21 H22 N2 O
CDES 2:E

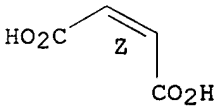
Double bond geometry as shown.



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

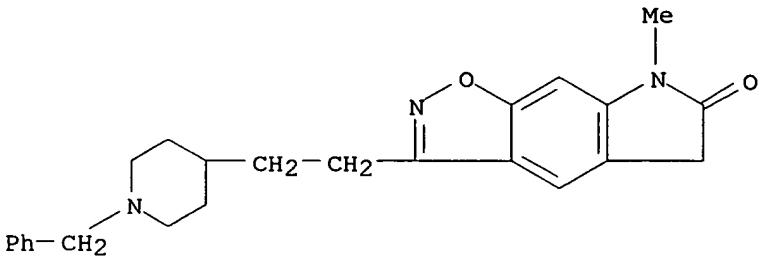
Double bond geometry as shown.



RN 145816-07-5 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

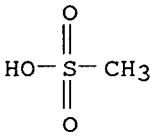
CM 1

CRN 145508-87-8
CMF C24 H27 N3 O2



CM 2

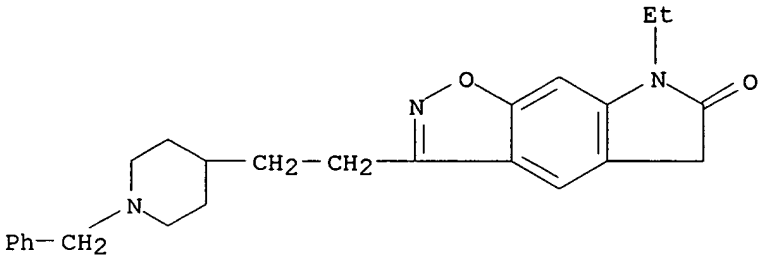
CRN 75-75-2
CMF C H4 O3 S



RN 145816-08-6 CAPLUS
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 7-ethyl-5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

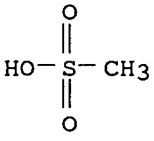
CM 1

CRN 145508-88-9
CMF C25 H29 N3 O2



CM 2

CRN 75-75-2
CMF C H4 O3 S



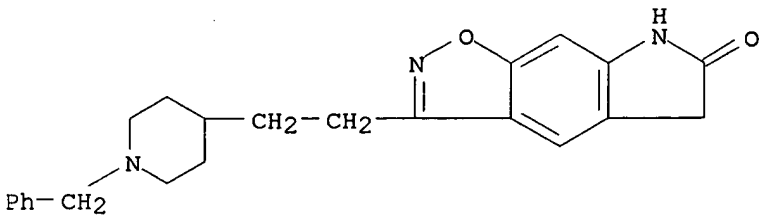
L171 ANSWER 21 OF 21 USPATFULL
ACCESSION NUMBER: 1999:72594 USPATFULL
TITLE: Processes and intermediates for preparing 5, 7-dihydro-3-[2-(1-benzylpiperidin-4-yl)ethyl-]6H-pyrrolo-[4, 5-F]-1, 2-benzisoxazol-6-one
INVENTOR(S): Devries, Keith M., Chester, CT, United States
Villalobos, Anabella, Niantic, CT, United States
PATENT ASSIGNEE(S): Pfizer Inc., NY, NY, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5916902	19990629	
	WO 9613505	19960509	
APPLICATION INFO.:	US 1997-836114	19970416	(8)
	WO 1995-IB755	19950913	
		19970416	PCT 371 date
		19970416	PCT 102(e) date

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chang, Ceila
LEGAL REPRESENTATIVE: Richardson, Peter C.; Ginsburg, Paul H.; Ling, Lorraine B.
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 435
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a process for preparing the compound having the formula ##STR1## which comprises i) heating the compound of formula ##STR2## wherein R.sup.3 is R.sup.4 or benzyl and R.sup.4 is R.sup.5 C(.dbd.O), R.sup.5 C(.dbd.O) or R.sup.5 SO.sub.2 wherein R.sup.5 is (C.sub.1 -C.sub.6)alkyl or (C.sub.6 -C.sub.10)aryl(C.sub.1 -C.sub.6)alkyl;

at an elevated temperature in the presence of a base with the proviso that when R.sup.3 in the resultant product is R.sup.4 said product is ii) further treated with an aqueous mineral acid at an elevated temperature followed by iii) treatment of the product of ii) with a) a benzylating agent in the presence of a base or b) benzaldohyde in the presence of a reducing agent and an acid.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **145508-78-7P**
(prepn. of a dihydro[(benzylpiperidinyl)ethyl]pyrrolobenzisoxazolone)
RN 145508-78-7 USPATFULL
CN 6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



FILE 'CAOLD' ENTERED AT 16:38:19 ON 20 MAR 2001
Searched by Barb O'Bryen, STIC 308-4291

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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L167        128 SEA FILE=REGISTRY SSS FUL L165
L170          0 SEA FILE=CAOLD ABB=ON  L167
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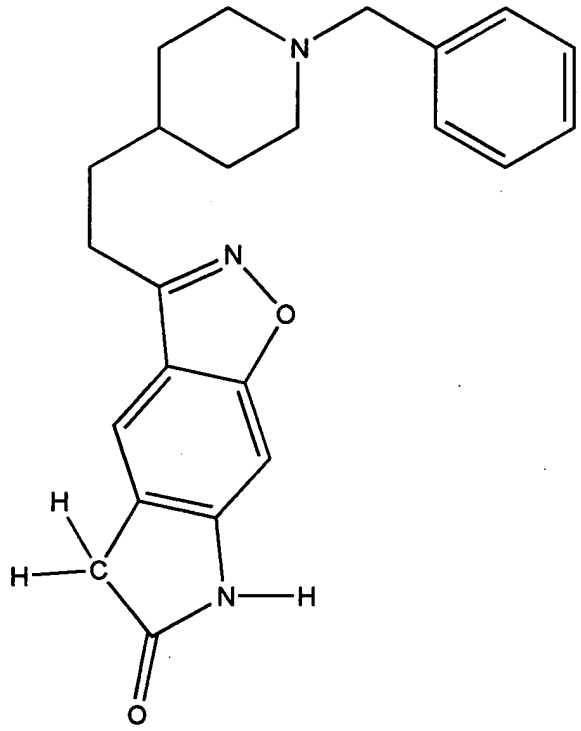
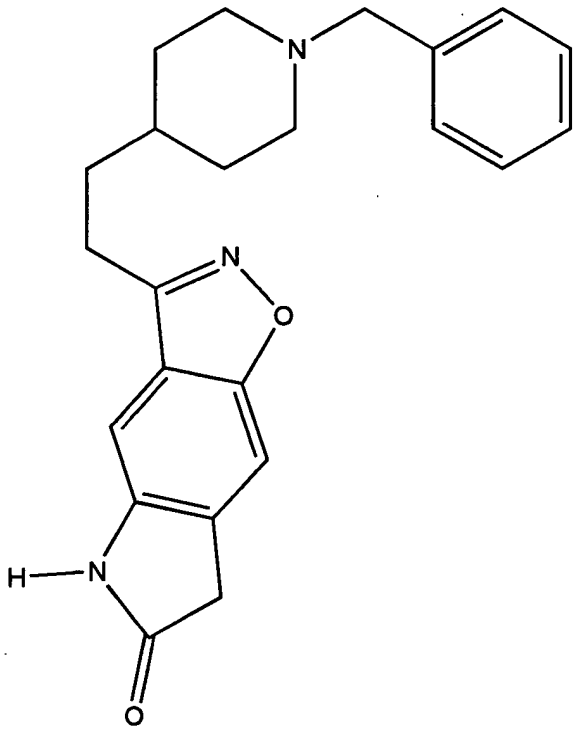


3-[2-(1-Benzyl-piperidin-4-yl)-ethyl]-5,7-dihydro-isoxazolo[4,5-*f*]indol-6-one



3-[2-(1-Benzyl-piperidin-4-yl)-ethyl]-5,7-dihydro-isoxazolo[5,4-*f*]indol-6-one

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=> fil reg; d que l177

FILE 'REGISTRY' ENTERED AT 17:17:04 ON 20 MAR 2001
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STRUCTURE FILE UPDATES:   19 MAR 2001  HIGHEST RN 328055-05-6
DICTIONARY FILE UPDATES:  19 MAR 2001  HIGHEST RN 328055-05-6

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

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  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

L172        292 SEA FILE=REGISTRY ABB=ON  NOC3-NC4-C6/ES
L173         24 SEA FILE=REGISTRY ABB=ON  L172 AND NC5/ES
L174         14 SEA FILE=REGISTRY ABB=ON  L173 AND C6/ES
L175        523 SEA FILE=REGISTRY ABB=ON  "C23 H25 N3 O2"/MF
L176          3 SEA FILE=REGISTRY ABB=ON  L174 AND L175
L177          2 SEA FILE=REGISTRY ABB=ON  L176 AND ONE(1W)5

=> d ide l177 1-2; fil capl; d que l178

L177 ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2001 ACS
RN   145508-78-7  REGISTRY
CN   6H-Pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-
     (phenylmethyl)-4-piperidinyl]ethyl]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   CP 118954
CN   Icopezil
FS   3D CONCORD
MF   C23 H25 N3 O2
CI   COM
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT, DDFU, DRUGNL, DRUGPAT, DRUGU,
       DRUGUPDATES, IPA, SYNTHLINE, TOXLIT, USAN, USPATFULL
     Other Sources:   WHO
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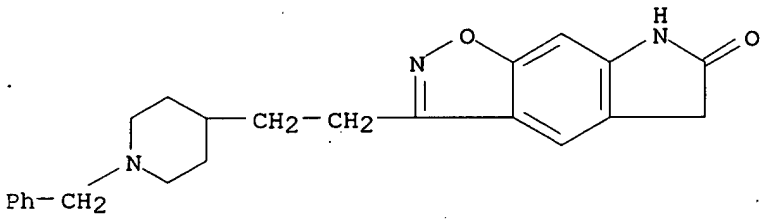


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              13 REFERENCES IN FILE CA (1967 TO DATE)
              13 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L177 ANSWER 2 OF 2  REGISTRY  COPYRIGHT 2001 ACS
RN   145508-69-6  REGISTRY
CN   6H-Pyrrolo[2,3-f]-1,2-benzisoxazol-6-one, 5,7-dihydro-3-[2-[1-
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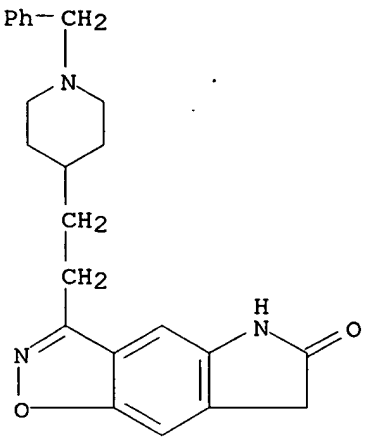
Searched by Barb O'Bryen, STIC 308-4291

(phenylmethyl)-4-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

FS 3D CONCORD
MF **C23 H25 N3 O2**
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

FILE 'CAPLUS' ENTERED AT 17:17:20 ON 20 MAR 2001

FILE COVERS 1967 - 20 Mar 2001 VOL 134 ISS 13
FILE LAST UPDATED: 19 Mar 2001 (20010319/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

The CA Lexicon is now available in the Controlled Term (/CT) field. Enter HELP LEXICON for full details.

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L172        292 SEA FILE=REGISTRY ABB=ON  NOC3-NC4-C6/ES
L173         24 SEA FILE=REGISTRY ABB=ON  L172 AND NC5/ES
L174         14 SEA FILE=REGISTRY ABB=ON  L173 AND C6/ES
L175        523 SEA FILE=REGISTRY ABB=ON  "C23 H25 N3 O2"/MF
L176          3 SEA FILE=REGISTRY ABB=ON  L174 AND L175
L177          2 SEA FILE=REGISTRY ABB=ON  L176 AND ONE(1W)5
L178         13 SEA FILE=CAPLUS ABB=ON  L177

=> s l178 not (l168 or 124)        previously printed

L183          0 L178 NOT (L168 OR L24)

=> d scan ti l178

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #6
TI    Radiotracers for in vivo study of acetylcholinesterase and Alzheimer's
      disease

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):13

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #7
TI    A pharmaceutical composition for the prevention and treatment of diseases
      of cognitive dysfunction in a mammal

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #11
TI    Automated docking of 82 N-benzylpiperidine derivatives to mouse
      acetylcholinesterase and comparative molecular field analysis with
      "natural" alignment

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 answer #1
TI    Preparation of benzisoxazoles and benzisothiazoles as cholinesterase
      inhibitors

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #2
TI    Methods of using piperidyl-benzisoxazole and benzisothiazole derivatives
      as cholinesterase inhibitors

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #16
TI    5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[3,2-f]-
      1,2-benzisoxazol-6-one: A Potent and Centrally-Selective Inhibitor of
      Acetylcholinesterase

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #5
TI    Treatment of age-related behavioral disorders of pets with acetylcholine
      esterase inhibitors, and pharmaceutical compositions containing
      piperidines for the treatment

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS
TI    Validation of protein-based alignment in 3D quantitative      L171 #8
      structure-activity relationships with CoMFA models

L178  13 ANSWERS   CAPLUS  COPYRIGHT 2001 ACS        L171 #9
TI    Combination of a GABAA.alpha.5 inverse agonist and an acetylcholinesterase
      inhibitor for treatment of neurodegenerative diseases
```

L178 13 ANSWERS CAPLUS COPYRIGHT 2001 ACS L171 #10
TI Combination of tetrahydropyridins and acetylcholinesterase inhibiting agents for treating senile dementia such as Alzheimer

L178 13 ANSWERS CAPLUS COPYRIGHT 2001 ACS L171 #13
TI Effect of drug particle size on content uniformity of low-dose solid dosage forms

L178 13 ANSWERS CAPLUS COPYRIGHT 2001 ACS L171 #14
TI Processes and intermediates for preparing 5,7-dihydro-3-[2-(1-benzylpiperidin-4-yl)ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one

L178 13 ANSWERS CAPLUS COPYRIGHT 2001 ACS L171 #20
TI Heterocyclic-cyclic amine derivatives, [(1-benzyl-4-piperidinyl)alkyl]benzisoxazoles and heteroaryl analogs, a method for their preparation and their use as cholinesterase inhibitors

ALL ANSWERS HAVE BEEN SCANNED

=> fil hom

FILE 'HOME' ENTERED AT 17:17:46 ON 20 MAR 2001